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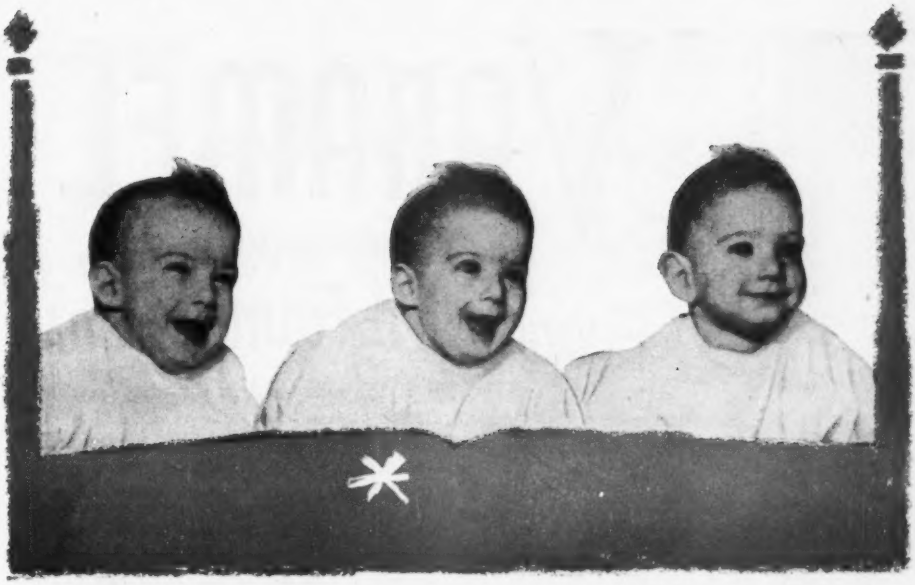

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*Sobel, S. H.: Milk Allergy in a case of Triplets, *Clin. Med.*, August 1952.

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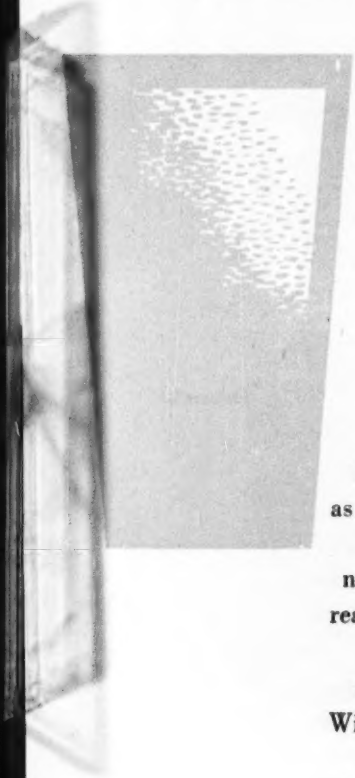

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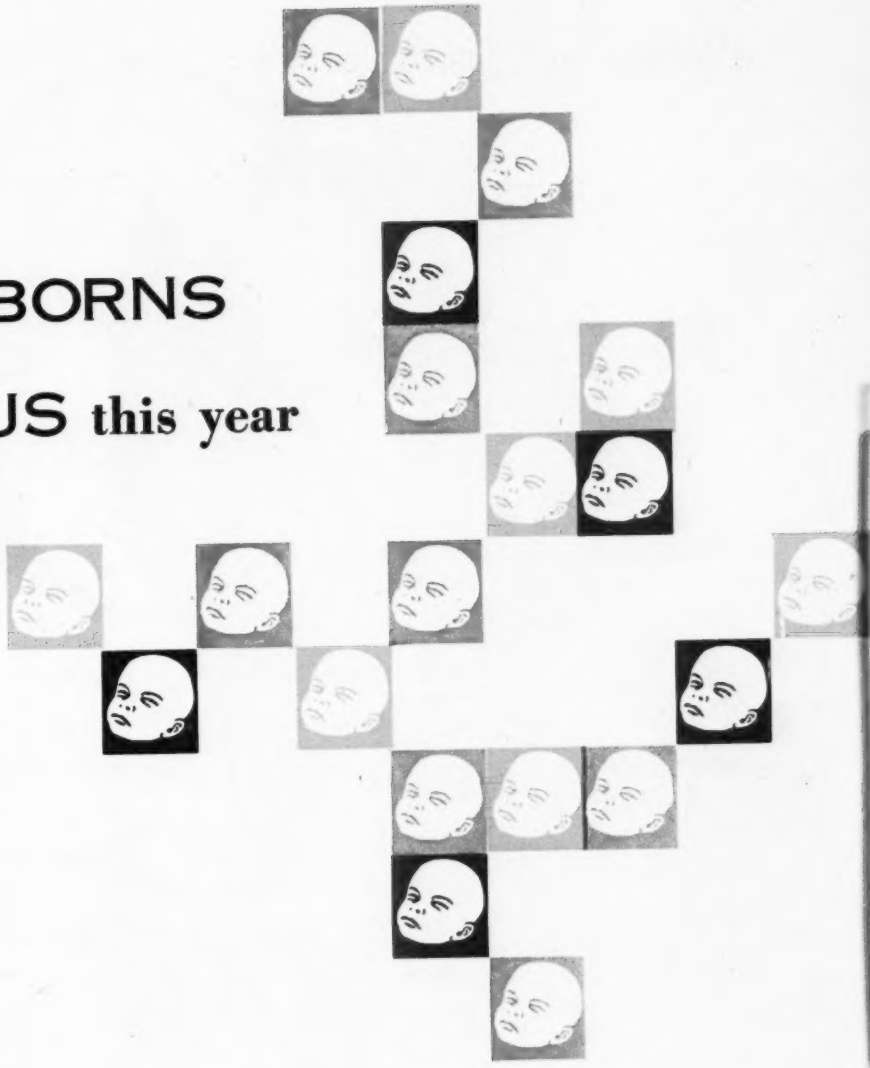

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1. Tisdall, F. F., and Jolliffe, N., in Clinical Nutrition, New York, P. B. Hoeber, 1950, c. 23, p. 590. 2. Sealock, R. R., and Goodland, R. L.: Science *114:* 645 (Dec. 14) 1951.

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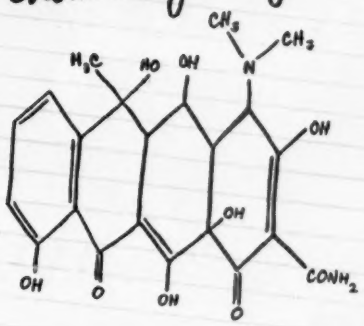

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FACTORS DETERMINING EFFECT OF INSULIN ON METABOLISM OF GLUCOSE IN ASCORBIC ACID DEFICIENCY AND SCURVY IN THE MONKEY

CHARLES T. STEWART, M.D.

ROBERT J. SALMON, M.Sc.

MINNEAPOLIS

AND

CHARLES D. MAY, M.D.

IOWA CITY

AS PART of an investigation of the adrenocortical function in scurvy, an attempt was made to use the effect of insulin on the level of glucose in the blood as one test of adrenocortical function. Selection of this test was based on the experience of Fraser and associates,[1] who demonstrated its usefulness in the evaluation of the adrenocortical function in humans. In adrenal insufficiency, insulin injected intravenously produces sustained hypoglycemia. When insulin was administered intravenously to scorbutic monkeys, the level of glucose in the blood was never more than slightly depressed and frequently actually rose. This response indicated an increase in the activity of the adrenal cortex, rather than a decrease. This is contrary to what might have been expected, considering the supposed role of ascorbic acid in adrenocortical function and its virtual absence from the adrenal gland in scurvy.

A review of the literature concerning the effect of insulin on glucose metabolism in scurvy failed to disclose data from which a ready explanation for this paradoxical response to insulin could be devised.

The experiments reported in this paper were undertaken to determine whether increased functioning of the adrenal cortex in scurvy was indeed the best explanation for the response to insulin. The data herein reported, coupled with data obtained from direct measurement of adrenocortical hormone production in scurvy,[2] provide evidence that the function of the adrenal cortex was not impaired in scurvy and that the gland was probably producing greater than normal amounts of hormone in response to the "stress" of scurvy.

Presented in part before the Society for Pediatric Research, May 5, 1952.

From the Department of Pediatrics of the Colleges of Medical Sciences of the University of Minnesota and State University of Iowa.

1. Fraser, R. W.; Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test, in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, J. Clin. Endocrinol. **1**:297-306, 1941.

2. Stewart, C. T.; Salmon, R. J., and May, C. D.: Function of the Adrenal Cortex in Ascorbic Acid Deficiency and Scurvy in the Monkey, J. Lab. & Clin. Med. **40**:657, 1952.

DIET AND MANIFESTATIONS OF THE ANIMALS

Immature rhesus monkeys, averaging 2.5 kg. in weight and estimated as approximately 15 months in age, were reared on a basal diet of cows' milk reconstituted with water to the normal composition. The milk was stored and boiled with copper sulfate to destroy the ascorbic acid. The diet of all monkeys was supplemented with iron, vitamins A, D, and E, vitamin B_{12}, and members of the B complex of vitamins other than folic acid (pteroylglutamic acid). More detailed accounts of the diet and manifestations of the animals appear in previous publications from this laboratory.[3]

"Control" monkeys received 50 mg. of ascorbic acid by mouth daily and thrived. Animals deprived of ascorbic acid remained vigorous and gained in weight for one to two months; a plateau in growth then occurred. During the first 30 days without ascorbic acid a marked decline in liver and adrenal ascorbic acid occurs.[4] Therefore, monkeys deprived of ascorbic acid for 30 days or more and exhibiting none of the gross signs of scurvy were considered to be "ascorbic-acid deficient." During the third month there followed progressive anorexia, loss of weight, roughening of the coat, and a decrease in general vigor. The joints became swollen and tender. Gross scurvy usually developed about 80 days after the exclusion of ascorbic acid from the diet and was frequently heralded by a burst of periorbital hemorrhages. Two to three weeks before this sign was present, characteristic x-ray changes were present in the long bones. Monkeys developing scurvy on this type of diet also regularly develop a marked deficiency of folic acid, usually about two weeks after the onset of scurvy, as revealed by a megaloblastic pattern in the bone marrow and decreased folic acid in the liver.[3] Scorbutic animals were designated as "scorbutic, normoblastic" prior to the development of megaloblastosis and "scorbutic, megaloblastic" afterward. It was therefore necessary to ascertain any effect of folic acid on the response to insulin in scurvy. As will be shown, folic acid had no effect. Subsequently, the diets of some animals were supplemented with folic acid. These have been so designated in the tables. Because the response to insulin was the same in the scorbutic animals whether folic acid was adequate or deficient, the data from the scorbutic animals were handled as groups based on the stage of scurvy rather than the presence of megaloblastosis. Megaloblastic animals have been clearly indicated in the tables in case any separate use of the data from this group should be desired.

An "adrenalectomized-control" animal was prepared by subjecting a control animal to a bilateral total adrenalectomy. This afforded the opportunity to obtain the response to insulin in the certain absence of adrenal hormones. The monkey was maintained on a regimen of adrenal hormones for the first three postoperative days. A dose of 50 mg. of ascorbic acid was continued daily. The regimen during

3. (*a*) May, C. D.; Sundberg, R. D.; Schaar, F.; Lowe, C. U., and Salmon, R. J.: Experimental Nutritional Megaloblastic Anemia: Relation of Ascorbic Acid and Pteroylglutamic Acid: Nutritional Data and Manifestations of the Animals, A. M. A. Am. J. Dis. Child. **82**:282-309, 1951. (*b*) May, C. D.; Hamilton, A., and Stewart, C. T.: Experimental Nutritional Megaloblastic Anemia and Scurvy in the Monkey: IV. Vitamin B_{12} and Folic Acid Compounds in the Liver, Diet, Urine, and Feces and Effects of Therapy, Blood **7**:978, 1952.

4. Footnote.[3b] May, C. D.; Hamilton, A., and Stewart, C. T.: Experimental Megaloblastic Anemia and Scurvy in the Monkey: V. Nature of the Relation of Ascorbic Acid Deficiency to the Metabolism of Folic Acid Compounds, J. Nutrition, Dec., 1952.

experimentation consisted of three feedings a day of the basal milk diet to which NaCl (1.8 gm. per liter) and $NaHCO_3$ (1.4 gm. per liter) were added to provide an additional 50 mEq. of Na and 30 mEq. of Cl per liter of milk (500 to 600 cc. was consumed daily). General vigor was normal, and the weight stabilized slightly below the preoperative value. The administration of corticotropin seven and eight months after adrenalectomy failed to produce a decline in the level of eosinophiles in the peripheral blood or an increase in the urinary excretion of 17-ketosteroids. The monkey was sacrificed 11 months after adrenalectomy, and a thorough postmortem examination failed to disclose gross or microscopic evidence of any accessory adrenal tissue or remnants of either adrenal gland.

METHODS

Insulin-tolerance Tests.—Insulin-tolerance tests were performed in the following manner: The animal was fasted 14 hours, and a sample of blood was obtained. Crystalline insulin, 0.1 unit per kilogram of body weight, was injected intravenously. The insulin was diluted in

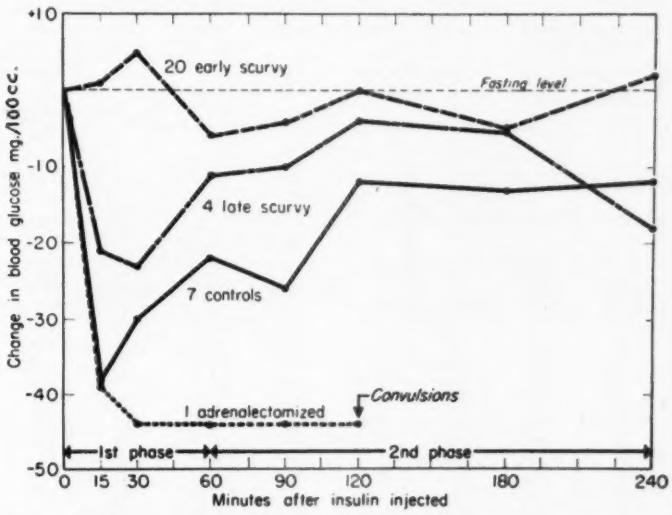

Chart 1.—Effect on blood glucose of 0.1 unit of insulin per kilogram of body weight injected intravenously in different groups of experimental animals; graph prepared from data in Tables 1, 2, and 3.

isotonic sodium chloride solution just prior to injection to facilitate the administration of this small amount of insulin. Samples of blood were obtained 15, 30, 60, 90, 120, 180, and 240 minutes after the injection of insulin. Blood was drawn from the femoral vein, and the level of glucose was determined immediately by the micromethod of Somogyi.[5] A few animals with severe anorexia received about 100 cc. of the milk by gavage daily for two to three days before testing to avoid the effects of starvation on stores of glycogen.

RESULTS

Controls and Adrenalectomized Control.—Seven control animals were tested, and each exhibited an initial depression of blood glucose with a subsequent return toward the fasting level. When the adrenalectomized-control animal (Monkey 52) was

5. Somogyi, M.: Determination of Blood Sugar, J. Biol. Chem. **160**:69-73, 1945.

tested 25 days after adrenalectomy, the depression of blood glucose was marked, and no recovery was apparent after two hours. The test was terminated at this time because of convulsions, which responded to intravenous administration of dextrose. The data are provided in Table 1 and graphically presented in Chart 1. These

TABLE 1.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously*

Monkey No.	Condition	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Cc.						
33	Control	95	−43	−60	−63	−60	−45	−21	−35
118	Control	98	−41	+10	−18	−40	−31	−26	−16
145	Control	104	−65	−67	−36	−34	−27	−39	−39
146	Control	74	−13	−11	+18	+12	+16	− 6	− 4
147	Control	70	−27	+ 3	+ 7	+ 2	+10	+16	+16
148	Control	72	−14	−30	−47	−26	− 5	−10	− 5
150	Control	82	−62	−53	−14	−33	0	− 3	− 3
	Average change in blood glucose		−38	−30	−22	−26	−12	−13	−12
52	Adrenalectomized Control (25 Days Postoperatively)	55	−39	−44	−44	−44	−44	(Convulsions)	

TABLE 2.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously in Early Scurvy*

Monkey No.	Day of Scurvy	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Cc.						
127	1	78	−23	−17	− 8	+ 4	− 8	−11	0
129*	3	76	− 4	+ 1	+ 8	+ 2	+ 3	+14	+11
130	3	84	−19	+ 5	−20	−14	− 9	−12	− 9
126	5	86	−28	−22	−21	− 5	0	− 3	+ 2
120*	5	87	+54	+30	+ 7	+ 7	− 3	−13	+ 1
106*	5	78	+50	+30	− 4	+ 6	− 2	− 1	0
127*	10	99	+35	+47	+ 1	+ 9	+18	−19	− 6
113*	11	56	+26	+20	+14	+ 7	+35	+16	+36
131	11	85	−20	−33	−34	−35	−14	− 6	− 5
130*	12	86	+ 4	−11	+ 8	−12	−11	− 5	+13
124*	14	78	+19	+ 6	−29	−29	−31	−25	−10
128*	15	65	+10	+20	+ 8	+ 7	+15	+ 2	+24
132	16	87	− 8	−10	−13	+ 4	− 9	0	+ 1
107*	20	59	+23	+26	− 2	− 9	+15	− 3	− 7
126	24	78	−20	−14	−11	....	....	....	....
132*	25	70	+16	+24	+14	....	....	....	....
126	29	76	−36	−21	−18	−21	− 4	− 4	−17
131	30	76	−17	−14	− 7	+ 4	0	+ 5	+ 4
126*	31	65	−25	+30	− 4	− 3	− 7	−20	− 5
131*	33	82	− 9	+ 4	− 1	+ 4	− 1	− 5	0
	Average change in blood glucose		+ 1	+ 5	− 6	− 4	0	− 5	+ 2

* Indicates "scorbutic, megaloblastic"; others are "scorbutic, normoblastic"; see text regarding lack of effect of folic acid deficiency on response to insulin.

responses to intravenous administration of insulin are similar to those obtained in normal and adrenal-insufficient humans.[1]

Early and Late Scurvy.—As scurvy appeared and progressed, the response to insulin departed from the normal. Two distinct and different types of response to

insulin were obtained in grossly scorbutic animals. During "early scurvy" (scorbutic less than 35 days) the blood glucose was never more than slightly depressed by insulin, and frequently actually rose (Table 2 and Chart 1). Twenty insulin-tolerance tests were performed on 12 monkeys in this early phase of scurvy, and each animal responded in this manner. It will be noted that Monkeys 127, 130, 126, 131, and 132 exhibited normal responses to insulin when first tested during "early scurvy," but each subsequently displayed a typically abnormal response. During

TABLE 3.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously in Late Scurvy*

Monkey No.	Day of Scurvy	Fasting Blood Glucose, Mg./100 Ce.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Ce.						
144*	36	59	−7	−21	−24	−23	−2	....	....
131†	37	70	−24	−4	−11	+6	−5	+2	−18
126†	38	56	−26	−27	+16	−12	−3	−7	−20
131†	39	97	−26	−46	−26	....	....	....	....
	Average change in blood glucose		−21	−23	−11	−10	−3	−5	−19

* Supplementary folic acid; "scorbutic, normoblastic."
† Scorbutic, megaloblastic; see text regarding lack of effect of folic acid deficiency on response to insulin.

TABLE 4.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously in Ascorbic Acid Deficiency*

Monkey No.	Days Without Ascorbic Acid	Fasting Blood Glucose, Mg./100 Ce.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Ce.						
130	32	94	−42	−41	−17	−3	−8	0	+4
128	37	109	−71	−77	−79	−81	−56	−61	−33
135	37	70	−3	−31	−28	−8	−4	−9	−11
133	37	51	+28	+12	−9	+4	+5	−2	−4
129	39	112	−56	−49	−23	−19	−24	−20	−34
127	42	113	−60	−60	−61	−56	−53	−54	−54
129	45	66	−16	0	+1	0	+16	+7	+33
127	50	65	−20	−24	−15	+1	+13	+11	+7
109	51	92	+18	+52	−18	+52	+9	−10	+32
121	53	85	+9	−9	−45	−41	−35	−23	−18
122	53	102	−29	−66	−18	−21	−23	−27	−21
	Average change in blood glucose		−22	−26	−28	−16	−15	−17	−9

"late scurvy" (scorbutic longer than 35 days) a moderate initial depression of blood glucose was followed by a prompt return toward the fasting level. Insulin had produced little or no depression of blood glucose when administered to these same animals in early scurvy (Table 3 and Chart 1).

Ascorbic Acid Deficiency.—Nine "ascorbic-acid-deficient" monkeys received insulin by intravenous administration, and five responded like the control animals. Four exhibited responses similar to those obtained in "early scurvy," and, of these, three occurred after ascorbic acid had been absent from the diet for 45 days or more (Table 4).

Sham Procedures in Controls and in Monkeys with Early Scurvy.—As manipulation attending venipunctures produced considerable excitement in the monkey tested,

sham procedures were performed to determine the effect of this excitement on the blood glucose. The animal was fasted 14 hours, and a specimen of blood was obtained. Isotonic sodium chloride solution, 0.1 cc. per kilogram of body weight, was injected intravenously, and samples of blood were obtained 15, 30, and 60 minutes after injection. Both a control animal and a monkey with "early scurvy" exhibited an initial hyperglycemia with a subsequent return toward the fasting level. The magnitude of the rise in blood glucose was greater in the control monkey.

To determine whether this hyperglycemia was due to the endogenous elaboration of epinephrine, sham procedures were performed in which 0.2 mg. of dihydroergocornine methanesulfonate per kilogram of body weight was administered intravenously simultaneously with the isotonic sodium chloride solution. This compound is known to block the hyperglycemic action of epinephrine.[6] Under these circumstances the control animal displayed a hyperglycemia of less degree than after administration of isotonic sodium chloride solution alone; in a monkey with "early scurvy" a slight hypoglycemia occurred (Table 5).

TABLE 5.—*Effect on Blood Glucose of Sham Procedures*

Monkey No.	Condition	Fasting Blood Glucose, Mg./100 Cc.	Min. After Normal Saline Solution Injected Intravenously: Change in Blood Glucose, Mg./100 Cc. 15	30	60
148	Control	87	+38	+62	+15
124	Early scurvy	89	+15	+10	+10
			Minutes After Normal Saline Solution and Dihydroergocornine Methanesulfonate Injected Intravenously		
148	Control	89	+47	0	—40
129	Early scurvy	82	— 4	0	— 3

Effects of Various Substances on Abnormal Response to Insulin in Early Scurvy.—The abnormal response to insulin in "early scurvy" might be due to an increase in the activity or elaboration of substances elevating the level of glucose in the blood or a deficiency of substances necessary for the normal action of insulin. Of those substances known to elevate the blood glucose, epinephrine, cortisone, and the hyperglycemic-glycogenolytic factor of the pancreas were tested. An attempt was made to determine if ascorbic acid, folic acid, or reduced glutathione would enhance the action of insulin in "early scurvy."

Epinephrine Tolerance Tests.—Epinephrine-tolerance tests were performed in a control animal and monkeys with "early scurvy" and "late scurvy" to detect any alteration in the activity of epinephrine. After a 14-hour fast a sample of blood was obtained. Epinephrine hydrochloride (1 : 1000), 0.03 cc. per kilogram of body weight, was injected subcutaneously, and the blood glucose was determined 15, 30, and 60 minutes after the injection. In the control animal the level of glucose in the blood rose progressively throughout the test period. Monkeys with "early scurvy"

6. Komrad, E. L., and Loew, E. R.: Inhibition of Epinephrine-Induced Hyperglycemia with Adrenergic Blocking Drugs, Am. J. Physiol. **165**:66-72, 1951.

and "late scurvy" exhibited an initial rise and a subsequent fall in blood glucose. The magnitude of the rise in blood glucose was similar in the early and late phases of scurvy and was greatest in the control monkey. Dihydroergocornine, 0.2 mg. per kilogram of body weight, administered intravenously simultaneously with the

TABLE 6.—*Effect on Blood Glucose of 0.03 Cc. of Epinephrine Hydrochloride (1: 1,000) per Kilogram of Body Weight Injected Subcutaneously*

Monkey No.	Condition	Fasting Blood Glucose, Mg./100 Cc.	Min. After Epinephrine Injected: 15	30	60
			Change in Blood Glucose, Mg./100 Cc.		
140	Control	76	+84	+109	+122
152	Early scurvy	62	+84	+113	+ 74
160	Early scurvy	63	+58	+ 70	+ 49
	Average change in blood glucose		+71	+ 92	+ 62
126	Late scurvy	64	+65	+ 85	+ 28
131	Late scurvy	83	+79	+ 98	+ 62
	Average change in blood glucose		+72	+ 89	+ 45
			Min. after Injection of Dihydroergocornine and Epinephrine Methanesulfonate		
140	Control	80	−11	− 14	− 15
152	Early scurvy	78	+38	+ 52	+ 22

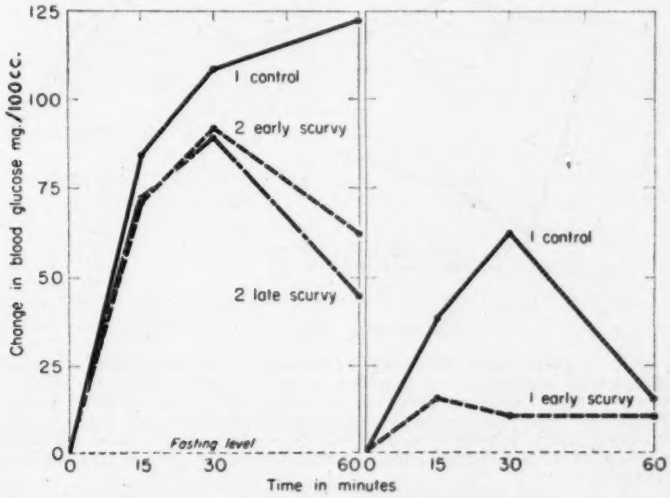

Chart 2.—First graph shows effect on blood glucose of 0.03 cc. of epinephrine hydrochloride (1:1,000) per kilogram of body weight injected subcutaneously; second graph shows effect of sham procedure. Graphs prepared from data in Tables 5 and 6. Note that in corresponding groups of animals hyperglycemia from administered epinephrine was of greater magnitude than that occurring in sham procedures assumed to be due to endogenously elaborated epinephrine.

epinephrine, which was administered as in an epinephrine-tolerance test, prevented the hyperglycemia in the control monkey and reduced it in a monkey with "early scurvy" (Table 6). It is of interest to note that in corresponding groups of

animals the hyperglycemia during the epinephrine-tolerance tests was of greater magnitude than during the sham procedures (Chart 2).

Epinephrine-Insulin Tolerance Test.—In a combined epinephrine-insulin tolerance test, epinephrine was injected subcutaneously simultaneously with the insulin, which was administered as in an insulin-tolerance test. In a control monkey receiving 0.03 cc. of epinephrine per kilogram of body weight, the response was like that

TABLE 7.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously with Simultaneous Administration of Epinephrine Subcutaneously*

Monkey No.	Condition	Epinephrine, Cc./Kg. of Body Weight	Fasting Blood Glucose, Mg./100 Cc.	Min. After Injection of Insulin and Epinephrine: 15	30	60
				Change in Blood Glucose, Mg./100 Cc.		
147	Control	0.03	91	−52	−32	−35
141	Control	0.15	72	+ 6	−12	−17

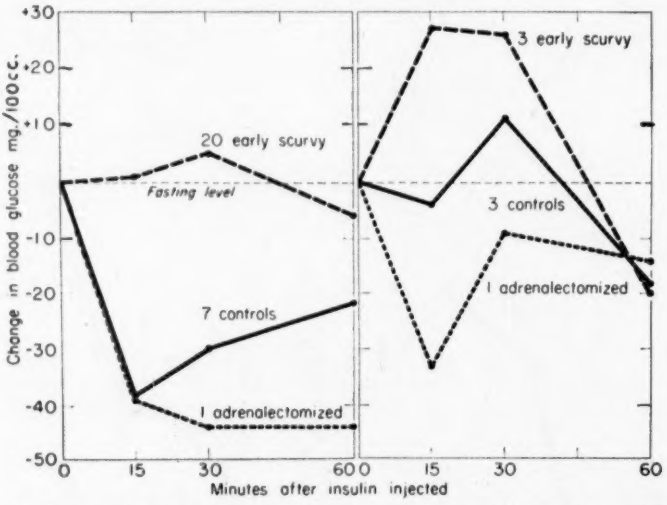

Chart 3.—First graph shows effect on blood glucose of 0.1 unit of insulin per kilogram of body weight injected intravenously in untreated animals; second graph shows effect on animals pretreated with 6 mg. of cortisone per kilogram of body weight for six days. Pretreatment of control animals with cortisone resulted in curves mimicking findings in "early scurvy," accentuated the hyperglycemic response in animals with "early scurvy" so treated, and modified curve in adrenalectomized-control to type seen in untreated controls. Graphs prepared from data in Tables 1, 2, and 8.

observed after insulin alone. When 0.15 cc. of epinephrine per kilogram of body weight was administered simultaneously with insulin, a control animal exhibited a response similar to that noted in "early scurvy" (Table 7).

Effect of Pretreatment with Cortisone on Response to Insulin.—The response to insulin was measured in control monkeys, monkeys with "early scurvy," and an "adrenalectomized-control" monkey after the intramuscular administration of 3 mg. of cortisone ("cortone acetate") per kilogram of body weight twice daily for six

days. Control animals pretreated with cortisone reacted to insulin like monkeys with "early scurvy"; in two animals (Monkeys 151 and 156) the level of glucose in the blood was only slightly depressed, and in the third (Monkey 142) an initial hyperglycemia occurred. After cortisone therapy two of the monkeys with "early scurvy" (Monkeys 127 and 132) exhibited a marked initial hyperglycemia with little depression of the blood glucose throughout the remainder of the test period. In the third animal with "early scurvy" (Monkey 107) an elevation of the fasting level of glucose in the blood was observed. The administration of insulin was followed by a gradual eventually marked decline of blood glucose. A return toward

TABLE 8.—*Effect of Pretreatment with Cortisone* on Response to 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously*

Monkey No.	Condition	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60
			Change in Blood Glucose, Mg./100 Cc.		
142	Control	108	+19	+16	−29
151	Control	88	−12	−16	−25
156	Control	64	−19	+32	0
	Average change in blood glucose		− 4	+11	−18
107	Early scurvy	116	− 4	−25	−56
127	Early scurvy	82	+35	+74	+ 9
132	Early scurvy	72	+49	+29	−15
	Average change in blood glucose		+27	+26	−21
52	Adrenalectomized-control (88 days postoperatively)	81	−33	− 9	−14

* Three mg./kg. of body weight twice a day for 6 days.

TABLE 9.—*Effect of Stress on Response to Insulin Injected Intravenously*

Monkey No.	Condition	"Stress"	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60	90	120	180	240
				Change in Blood Glucose, Mg./100 Cc.						
134	Control	Dysentery	135	−3	− 9	−7	−10	+27	−44	+ 8
118	Control	Turpentine abscess	87	−1	−10	−5	+12	+10	+12	−13
Average change in blood glucose				−2	−10	−6	+ 1	+19	−16	− 3

the fasting level was noted in the four-hour specimen. Pretreatment of the "adrenalectomized-control" animal (Monkey 52) with cortisone 88 days after adrenalectomy resulted in a normal response to insulin (Table 8 and Chart 3).

Effect of Stress on Response to Insulin.—Because of the similarity in response to insulin between monkeys with "early scurvy" and control animals pretreated with cortisone, the response to insulin was measured in monkeys with increased adrenocortical activity induced by stress. A control animal which became acutely ill from a type of dysentery exhibited only slight depression of blood glucose after administration of insulin. A similar response was obtained in a control monkey

in which the stress was caused by a sterile abscess produced by turpentine (Table 9). The injection of turpentine also produced a marked eosinopenia and an elevation in the spontaneous urinary excretion of 17-ketosteroids.

Effect on Blood Glucose of an Insulin Preparation Devoid of the Hyperglycemic-Glycogenolytic Factor.—Banerjee reported hyperplasia of the alpha cells of the pancreas in the scorbutic guinea pig.[7] These cells are one source of a hyperglycemic-glycogenolytic factor, which is present in small amounts in the standard commercial crystalline insulin.[8] Therefore, the response to an insulin preparation devoid of this factor[9] was measured. Control animals exhibited the usual initial hypoglycemia with subsequent return toward the fasting level. One monkey with "early scurvy" exhibited a marked initial hyperglycemia, while another developed a slight transient hypoglycemia (Table 10).

TABLE 10.—*Effect on Blood Glucose of 0.1 of Insulin Devoid of the Hyperglycemic Principle* per Kilogram of Body Weight Injected Intravenously*

Monkey No.	Condition †	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Cc.						
143	Control	75	−17	−36	−23	−10	− 7	−5	0
144	Control	70	−34	−47	−27	−18	−17	+6	0
Average change in blood glucose			−26	−42	−25	−14	−12	+1	0
143‡	Early scurvy	93	−18	− 2	−13	....	....	...	..
144‡	Early scurvy	74	+ 7	+68	+63	....	....	...	..
Average change in blood glucose			− 6	+33	+25	....	....	...	..

* See text for description of this preparation.
† Animals first tested as "controls," then ascorbic acid omitted and retested in "early scurvy."
‡ Supplementary folic acid, "scorbutic, normoblastic."

Effect of Ascorbic Acid on Response to Insulin in Scurvy.—Three monkeys with "early scurvy" received the usual amount of insulin intravenously and simultaneous injections of 200 mg. of ascorbic acid intravenously and 200 mg. intramuscularly. In two of the animals (Monkeys 127 and 128) the response noted was like that in early scurvy after insulin alone. Monkey 129 exhibited a moderate hypoglycemia with prompt recovery (Table 11 and Chart 4).

Whereas the simultaneous administration of insulin and ascorbic acid did not alter the response to insulin immediately in Monkey 128, a normal response was observed five days after this injection of ascorbic acid, when the clinical course was one of early-healing scurvy (Table 12).

7. Banerjee, S.: Vitamin C and Carbohydrate Metabolism: The Effect of Vitamin C on the Histology of the Pancreas of Guinea Pigs, Ann. Biochem. & Exper. Med. **4**:37-40, 1944.

8. Sutherland, E. W., and de Duve, C.: Origin and Distribution of the Hyperglycemic-Glycogenolytic Factor of the Pancreas, J. Biol. Chem. **175**:663-674, 1948.

9. This insulin preparation was generously supplied by Dr. C. G. Weigand, Head of the Medical Department, Eli Lilly & Company Research Laboratories. The potency of the preparation (Lot No. 190-1B-11E) was the same as that of the standard commercial insulin (40 units per cubic centimeter). The hyperglycemic-glycogenolytic factor was removed by trypsin digestion.

TABLE 11.—*Effect on the Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously with the Simultaneous Administration of 400 Mg. of Ascorbic Acid Intramuscularly and Intravenously*

Monkey No.	Condition	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin and Ascorbic Acid Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Cc.						
127	Early scurvy	90	+14	+20	+10	−14	−35	−33	−53
128	Early scurvy	72	+ 4	+26	+ 6	+24	+25	+21	+ 3
129	Early scurvy	72	−17	−34	−18	−18	− 7	+ 9	+ 6
	Average change in blood glucose		0	+ 7	− 1	− 3	− 6	− 1	−15

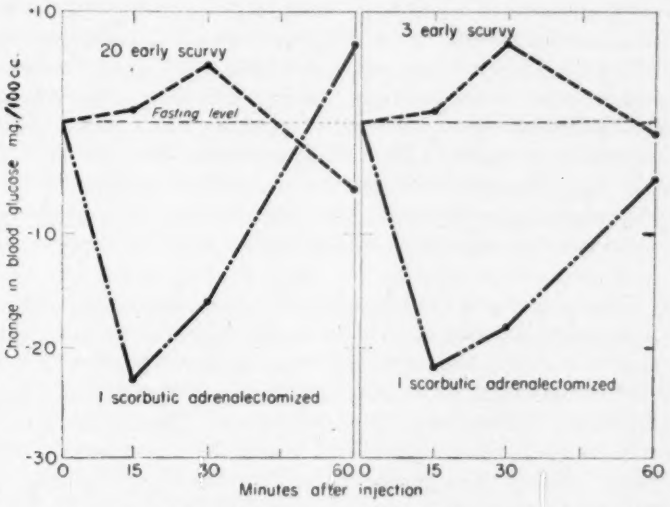

Chart 4.—First graph shows effect on blood glucose of 0.1 unit of insulin per kilogram of body weight injected intravenously; second graph shows effect of 400 mg. of ascorbic acid injected intramuscularly and intravenously simultaneously with insulin. Effect of insulin not enhanced by simultaneous injection of ascorbic acid in scorbutic monkeys. Normal response to insulin in adrenalectomized animal which had been rendered scorbutic was obtained 191 days after adrenalectomy. Significance of this discussed in text.

TABLE 12.—*Effect on Blood Glucose of 0.1 Unit of Insulin per Kilogram of Body Weight Injected Intravenously in Monkeys with Early Scurvy After Treatment with Ascorbic Acid*

Monkey No.	Ascorbic Acid Therapy	Fasting Blood Glucose, Mg./100 Cc.	Min. After Insulin Injected: 15	30	60	90	120	180	240
			Change in Blood Glucose, Mg./100 Cc.						
128	400 mg. intramuscularly and intravenously 5 days prior to test	75	−25	−32	−18	−15	−9	−7	+17
105	1 mg. intramuscularly daily								
	5 days	52	+51	+25	0	− 5	−2	+4	+14
	25 days	67	−15	−17	−24	−10	+1	−9	− 7

To ascertain the sequence of events following much smaller more physiological doses of ascorbic acid one animal with "early scurvy" (Monkey 105) was treated with 1 mg. of ascorbic acid administered intramuscularly daily (estimated daily requirement of monkeys for ascorbic acid).[10] Five days after the commencement of therapy there was no alteration in the response to insulin. A normal response was ultimately obtained after 25 days of treatment. By this time there was clinical evidence of partial recovery from scurvy (Table 12).

Effect of Pretreatment with Folic Acid on Response to Insulin in Scurvy.—Beginning on the 70th day without ascorbic acid, three animals (Monkeys 143, 144, 148) received 5 mg. of folic acid ("folvite") intramuscularly each week. This amount of folic acid is sufficient to prevent the megaloblastic anemia and depletion of liver folic acid which regularly occurs in scorbutic monkeys on milk diets.[3a] The response to insulin was measured when the animals reached the period of "early scurvy." In Monkeys 143 and 144 the response to an insulin preparation devoid of the hyperglycemic principle[9] was measured (Table 10). In the former a slight hypoglycemia occurred, while the latter exhibited a marked initial hyperglycemia. In Monkey 148, tested with regular insulin, the fasting blood glucose was elevated and the depression of blood glucose was slight (fasting, 162 mg. per 100 cc.; 15 minutes, 157 mg.; 30 minutes, 164 mg., and 60 minutes, 160 mg.).

Effect of Pretreatment with Reduced Glutathione on Response to Insulin in Scurvy.—The effect of reduced glutathione on the response to insulin in "early scurvy" was measured to ascertain (1) the role of sulfhydryl enzymes in the metabolism of glucose[11] and (2) possible interrelationships between adrenocortical steroids and glutathione,[12] and because of (3) the report that the blood glutathione is decreased in scurvy.[13] A monkey with "early scurvy" (Monkey 110) received 1 gm. of reduced glutathione intramuscularly daily for three days and an insulin-tolerance test was performed on the last day of therapy. The injection of insulin was followed by a hyperglycemic response like that noted in untreated animals with "early scurvy" (fasting blood glucose, 65 mg. per 100 cc.; 15 minutes, 102 mg.; 30 minutes, 86 mg., and 60 minutes, 66 mg.).

Observations in the Adrenalectomized-Control Monkey.—Several interesting observations were made concerning the adrenalectomized-control animal (Monkey 52) in the 11-month period following adrenalectomy, which suggest that "adaptation" had occurred in certain metabolic systems.

When tested 25 days postoperatively, the response to insulin was of the type commonly encountered in adrenal insufficiency. Subsequently, ascorbic acid was

10. Day, P. L.: The Nutritional Requirements of Primates Other Than Man, Vitamins & Hormones **2**:71-105, 1944.

11. Barron, E. S. G., and Singer, T. P.: Studies on Biological Oxidations: XIX. Sulfhydryl Enzymes in Carbohydrate Metabolism, J. Biol. Chem. **157**:221-240, 1945.

12. Conn, J. W.; Louis, L. H., and Johnston, M. W.: Metabolism of Uric Acid, Glutathione and Nitrogen and Excretion of "11-Oxysteroids" and 17-Ketosteroids During Induction of Diabetes in Man with Pituitary Adrenocorticotropic Hormone, J. Lab. & Clin. Med. **34**:255-269, 1949.

13. Banerjee, S.; Deb, C., and Belavady, B.: Effect of Scurvy on Glutathione and Dehydroascorbic Acid in Guinea Pig Tissues, J. Biol. Chem. **195**:271-276, 1952.

omitted from the diet, and the animal was rendered scorbutic. The response to insulin was obtained in "early scurvy" (191 days after adrenalectomy), and it was normal (Fig. 4). The administration of ascorbic acid simultaneously with insulin in this early phase of scurvy did not significantly alter the response to insulin (Fig. 4). Administration of ascorbic acid was resumed, and complete recovery from scurvy occurred. Responses to insulin obtained 264 and 285 days after adrenalectomy were also normal.

When deprived of additional salt 59 days after adrenalectomy, the monkey exhibited a marked obligatory polyuria and dehydration rapidly ensued. Later a severe dysentery also rapidly led to marked dehydration. Both of these episodes required parenteral fluid therapy. Two hundred sixty-five days after operation the animal withstood not only elimination of the added salt but also dilution of the milk diet to half strength for five days for a further reduction of electrolyte intake. During the last month before the monkey was killed it was maintained in good health on the basal milk diet without added salt.

The administration of corticotropin 210 and 246 days after adrenalectomy failed to produce a decline in the circulating eosinophiles or an increase in the urinary excretion of 17-ketosteroids.[2] However, a wound infection during the first month after adrenalectomy was associated with a marked eosinopenia.

In a final period of experimentation, 307 days after adrenalectomy, the animal withstood the severe stress of a sterile abscess produced by the injection of turpentine.

From these observations it was inferred that (1) remnants of the adrenal glands had been left at operation; (2) accessory adrenal tissue was present, or (3) adaptation had occurred even in the absence of the adrenal glands. Evidence against the first two possibilities is the failure to excrete increased hormones after administration of corticotropin (ACTH) and the fact that a thorough postmortem examination failed to disclose remnants of either adrenal gland or accessory adrenal tissue. Thus, it would appear that this animal was capable of adaptation to a variety of stresses even without its adrenal glands.

These observations do not invalidate the use of this animal as an "adrenalectomized control" in the insulin-tolerance test. This test was performed 25 days postoperatively, while the animal was still in the stage of acute adrenal insufficiency before adaptation. This time interval is comparable in duration to the average period of scurvy in the scorbutic monkeys tested.

COMMENT

The data presented are subject to the following interpretations: The relative lack of effect of insulin on blood glucose in "early scurvy" is referable to an increase in the elaboration of adrenocortical hormones (11-oxysteroids). This increase in the activity of the adrenal cortex is probably induced by the stress of the diffuse pathological changes in scurvy. The frequent occurrence of an actual hyperglycemia after insulin in "early scurvy" is attributable to the elaboration of epinephrine substances occasioned by the excitement of the test. This action of epinephrine substances is apparent only because of the reduced action of insulin and not because of an increase in the activity or amount of epinephrine substances elaborated. The

relatively normal response to insulin in "late scurvy" is indicative of a return of adrenocortical activity toward normal and may represent adaptation to the chronic stress of scurvy.

These interpretations are supported by reports in the literature indicating an increase in the activity of the adrenal cortex in the scorbutic guinea pig; they are as follows: (1) an increase in the pituitary concentration of corticotropin,[14] (2) hypertrophy of the adrenal gland,[15] (3) an increase in the spontaneous urinary excretion of 17-ketosteroids [16] and formaldehydogenic substances,[17] (4) an eosinopenia in the peripheral blood,[18] and (5) a reduced oral glucose tolerance.[19]

A decrease in the elaboration of adrenocortical hormones has been claimed to occur in scorbutic guinea pigs based on observations of the effects of administration of cortisone on the clinical course and gross pathology of scurvy.[20] Similar claims have been presented on a report by Herrick and associates, which includes data indicating that the administration of cortisone almost completely prevented the development of skeletal lesions in guinea pigs deprived of ascorbic acid.[21] Upton and Coon [18] and, more recently, Wolbach and Maddock [22] challenged these claims by presenting evidence that cortisone therapy does not alter the histopathology or clinical course of scurvy in the guinea pig.

Exhaustion of the adrenal cortex may occur as a terminal event in scurvy, but it would be difficult to deduce whether this is attributable to the lack of ascorbic acid per se or to the severe deterioration and metabolic disturbances of animals with advanced scurvy. A gradual adaptation to the stress of chronic scurvy would offer an additional obstacle to successful application of functional tests in this terminal phase of scurvy.

The vague and unsatisfactory character of the terms adaptation and stress are fully appreciated, but it is felt that the phenomena to which the terms refer are generally recognized.

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21. Herrick, E. H.; Mead, E. R.; Egerton, B. W., and Hughes, J. S.: Some Effects of Cortisone on Vitamin C-Deficient Guinea Pigs, Endocrinology **50**:259-263, 1952.

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SUMMARY

This study was undertaken to determine the effect of ascorbic acid deficiency on adrenocortical function. The effect of insulin on the level of glucose in the blood was chosen as a test of adrenocortical function. It was found that the dose of insulin which produced a pronounced depression of blood glucose in control monkeys had little effect in scorbutic monkeys. A series of experiments were performed analyzing the influence of epinephrine and cortisone on the response to insulin in scurvy. The data obtained indicate that adrenocortical function is increased in scurvy rather than decreased and that this accounts for the relative lack of effect of insulin on blood glucose in scurvy.

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WOLFF-PARKINSON-WHITE SYNDROME IN INFANTS AND CHILDREN

MARY ALLEN ENGLE, M.D.
NEW YORK

THE COMBINATION of a short P-R interval and a prolonged QRS duration on the electrocardiogram in frequent association with attacks of paroxysmal tachycardia was first recognized as a syndrome in 1930 by Wolff, Parkinson, and White.[1] Since that time several hundred cases have been reported. Most of the patients in these cases have been young adult males in good health except for the episodes of tachycardia.

Although the syndrome is not rare in the younger age group, the reported instances of this condition in infants and children to the age of 14 years are few.[2]

From the Department of Pediatrics of the New York Hospital, Cornell Medical Center.

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They are summarized in the table. Five additional cases, not reported in detail, were encountered in a study by Nadas and co-workers [3] of 41 infants and children seen during a 20-year period because of paroxysmal tachycardia. One probable example in a 4½-year-old boy was described by Ziegler.[4] Of the 26 patients whose sex was stated, 18 were males (Table). At the time the electrocardiograms were first recorded, the ages ranged from 8 days [2a] to 14 years.[2y] Six were one month of age or less,[5] and three others were 3½ to 6 months old.[6] At least 26 [7] of the 31 previously reported patients experienced attacks of paroxysmal tachycardia; indeed, it was the occurrence of these episodes that brought most of the children to medical attention. Two infants [8] and one older boy [2w] died as a result of the paroxysmal tachycardia.

Four infants and children with the Wolff-Parkinson-White syndrome have been followed at the New York Hospital for a period of 1½ to 10 years. One of these, the patient in Case 1, was only 6 days old when the preexcitation phenomenon was found in the electrocardiogram. Symptoms compatible with attacks of tachycardia dated from the first day of life. He is the youngest patient with this abnormality in cases yet recorded.

REPORT OF CASES

CASE 1.—R. J. M., was born in the New York Hospital on Dec. 2, 1950. During the first two days of life, transient cyanosis, a weak cry, and inspiratory and expiratory stridor with slight suprasternal retraction were noted. At the age of 54 hours he was found to be deeply cyanotic. His respirations were labored, and the stridor and retractions were more marked. In oxygen his color became less dusky; however, within two hours he appeared acutely ill. His temperature rose to 38.2 C. (100.8 F.). Rales were heard at the base of the left lung, but no cardiac murmurs were audible. The liver was not enlarged. On fluoroscopy of the chest no abnormalities were seen. An hour later the baby suddenly improved. His cyanosis and respiratory difficulty subsided, his temperature returned to normal, and he nursed well. Similar episodes occurred on the fifth and again on the sixth days. Because of these attacks he was transferred to the pediatric service.

Physical Examination.—His temperature was 37.2 C. (98.9 F.); pulse rate, 140; respiration, 28, and weight 3,000 gm. His color was good, and there was but slight suprasternal retraction. The lungs were clear. The heart sounds were normal, the rhythm regular, and there were no murmurs. The peripheral pulses were strong. The liver was not enlarged. Results of the remainder of the examination were unremarkable.

Paroxysmal Tachycardia and Bundle Branch Block in a Boy of 11, Acta pædiat. **18**:491, 1936. (*v*) Wolff, L., and White, P. D.: Syndrome of Short P-R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia, Arch. Int. Med. **82**:446, 1948. (*w*) Wood, F. C.; Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, Am. Heart J. **25**:454, 1943. (*x*) Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome with Paroxysms of Ventricular Tachycardia, Am. Heart J. **22**:401, 1941. (*y*) Bishop, L. F., Jr.: Bundle Branch Block with Short P-R Interval in Individuals Without Organic Heart Disease: Case Report with Review of Literature, Am. J. M. Sc. **194**: 794, 1937.

3. Nadas, A. S.; Daeschner, C. W.; Roth, A., and Blumenthal, S. L.: Paroxysmal Tachycardia in Infants and Children: Study of 41 Cases, Pediatrics **9**:167, 1952.

4. Ziegler, R. F.: Electrocardiographic Studies in Normal Infants and Children, Springfield, Ill., Charles C Thomas, Publisher, 1951, pp. 20, 28, and 29.

5. Footnote 2 *a*, *b*, *c*, *e*, *f*, and *g*.

6. Footnote 2 *h*, *i*, and *j*.

7. Footnotes 1, 2 *a*, *b*, *c*, *d*, *g*, *h*, *i*, *j*, *k*, *l*, *m*, *n*, *o*, *p*, *q*, *s*, *u*, *w*, *x*, and *y*, and 3.

8. Footnote 2 *b* and *g*.

Reported Instances of Wolff-Parkinson-White Syndrome in Infants and Children

Author	Age of Patient When Wolff-Parkinson-White Syndrome First Recorded	Sex	Axis Deviation With Wolff-Parkinson-White Complexes: Right	Left	None	?	Spontaneous Occurrence of Normal Complexes	Episodes of Paroxysmal Tachycardia	Comment
Engle	6 days	M	+	..	..	..	+	+	.....
Arvola [2a]	8 days	M	+	+	..	..	+	+	Right axis deviation in a newborn infant; left axis deviation at 1 yr.
Silverman & Werner [2b]	11 days	M	+	..	..	..	0	+	Death at 7 weeks in heart failure after an attack of paroxysmal tachycardia; no autopsy
Mannheimer [2c]	3 wk.	M	+	..	..	..	+	+	Included in Landtman's monograph [2d]
Nádrai [2e]	3 wk.	?M	..	+	..	..	+	?	.....
Schieve [2f]	5 wk.	F	..	+	..	..	0	+	.....
Kimball & Burch [2g]	1 mo.	M	+	..	..	..	+	+	Death in attack of paroxysmal tachycardia; aberrant bundles of tissue found post mortem
Bodlander [2h]	3½ mo.	M	..	+	..	..	+	+	Thought to have coarctation of aorta
Richmond, Moore & Callen [2i]	4½ mo.	F	+	..	..	..	+	+	.....
Christensen [2j]	6 mo.	M	..	+	..	..	0	+	Also reported by Jörgensen [2k]
Engle	15 mo.	F	..	+	..	..	+	+	.....
Lindgren [2l]	1 yr.	F	..	+	..	..	0	+	Followed to age of 10 years
Öhnell [2m]	2 yr.	M	..	..	..	+	+	+	Familial incidence
Engle	3½ yr.	F	..	+	..	..	0	+	.....
Hamburger [2n]	4½ yr.	M	..	+	..	..	+	+	Twenty-year follow-up by Malinow and Langendorf [2o]
Kleiber [2p]	6 yr.	M	..	..	+	..	0	+	First attack of tachycardia at 7 months; because of basal systolic murmur and normal heart size thought to have ventricular septal defect
Nádrai [2e]	6 yr.	M	..	..	+	..	+	?	.....
Kiss [2q]	6½ yr.	M	..	+	..	..	0	+	.....
Aastrup [2r]	7 yr.	?	..	..	..	+	?	?	Quoted by Jörgensen [2k]
Butterworth & Poindexter [2s]	9 yr.	F	..	+	..	..	0	+	Followed 15 years
Bain & Hamilton [2t]	10 yr.	M	..	..	..	+	0	0	Only leads 2 and 3 reproduced
Engle	10 yr.	M	..	+	..	..	0	+	.....
Wolff-Parkinson, White [1]	11 yr.	M	+	..	..	..	0	+	.....
Faxén [2u]	11 yr.	M	..	+	..	..	0	+	.....
Landtman [2d]	13 yr.	F	..	..	..	+	+	+	.....
Wolff & White [2v]	13 yr.	F	..	+	..	..	+	0	.....
Wood, Wolferth & Geckeler [2w]	13 yr.	M	+	..	..	..	0	+	Death during paroxysm of tachycardia; accessory atrioventricular connections at right heart border found post mortem
Levine & Beeson [2x]	13 yr.	M	..	+	..	..	0	+	Attack of paroxysmal ventricular tachycardia
Bishop [2y]	14 yr.	M	..	..	+	..	+	+	.....

Laboratory Studies.—An electrocardiogram at the age of 6 days revealed a Wolff-Parkinson-White syndrome (Fig. 1). Fluoroscopy of the heart in the anteroposterior and both oblique views revealed no abnormalities. With barium swallow, there was seen a left aortic arch and descending aorta. The left auricle was not enlarged, and there were no retroesophageal vessels. The chest roentgenogram, which confirmed this impression, demonstrated small areas of patchy atelectasis of the lungs. The blood count was normal for a newborn infant; it was as follows: hemoglobin, 23.8 gm. per 100 cc.; red blood count 5,700,000, and white blood count 10,800, with a normal differential count. Values on urinalyses were normal. The CO_2-combining power was 19.8 mm. per liter. The blood culture was sterile, and nose and throat cultures were negative for pathogens.

Course.—When he was 8 days old, an electrocardiogram was recorded during an episode of paroxysmal supraventricular tachycardia at a rate of 295 per minute (Fig. 2). The QRS complexes were of normal form and duration (0.04 second). Four hours later, another electrocardiogram showed the spontaneous return of sinus rhythm. At this time there was a normal P-R interval of 0.11 second and a QRS interval of 0.04 second. As the unipolar limb leads were being recorded, the Wolff-Parkinson-White complexes returned (Fig. 3).

When 17 days of age, during a febrile respiratory illness, he had a sinus tachycardia of 210 per minute with normal P-R and QRS intervals. After the age of 3 weeks no further episodes of tachycardia were observed. The electrocardiograms from the 3rd to 6th weeks showed at times normal conduction and on other occasions the preexcitation phenomenon.

Since his discharge from the hospital, he has been followed at monthly intervals in the clinic for well-baby care. All subsequent electrocardiograms have been normal as to rate, rhythm, and conduction times, and his heart has been normal on physical examination and on fluoroscopy. When last seen, at the age of 18 months, he appeared to be a healthy active infant.

CASE 2.—J. G., was admitted on April 12, 1943, at the age of 15 months, because of vomiting and swelling of the eyelids and abdomen.

Present Illness.—The attending obstetrician stated that the baby's heart rate was remarkably rapid and suggested that it be investigated. On numerous occasions thereafter the parents commented on the rapidity of the heart beat. Bouts of vomiting started during the first month and recurred every two to three months.

Eleven days prior to admission the child appeared apathetic and began to vomit. Her temperature rose to 103 F. Four days later, a paroxysmal cough and swelling of the dorsa of her hands were noted. The day prior to admission swelling of the eyelids and abdomen appeared.

Physical Examination.—Her temperature was 37.4 C. (99.3 F.); pulse rate, 280; respiration, rapid and labored; blood pressure, 90/58 mm. Hg, and weight, 12,900 gm. She was pale and fretful, yet listless. There was no cyanosis. The heart was enlarged. The heart sounds were regular, were exceedingly rapid, and were "tic tac" in quality. No murmurs were heard. There were no rales in the lungs. The abdomen was prominent; the enlarged and tender liver extended to the level of the umbilicus. There was periorbital edema as well as slight edema of the extremities. The findings on examination otherwise were within normal limits.

Laboratory Studies.—An electrocardiogram on admission showed paroxysmal supraventricular tachycardia with a rate of 280 per minute (Fig. 4*B*). The chest x-ray revealed diffuse cardiac enlargement. There was, however, no pulmonary congestion. The hemoglobin value was 11 gm. per 100 cc.; red blood count, 4,500,000, and the white blood count 21,000, with a slight shift to the left. Findings on urinalysis and stool examination were normal, and the nose and throat cultures were negative for pathogens.

Course.—She was given 0.1 gm. of digitalis on admission and again six hours later. Three hours after the second dose, her pulse rate dropped to 120 per minute, and an electrocardiogram recorded a regular sinus rhythm but revealed a Wolff-Parkinson-White syndrome (Fig. 4*A*). With the cessation of the tachycardia the signs of cardiac decompensation disappeared. When the digitalis treatment was discontinued, her pulse remained slow and regular. On two occasions the effect of atropine sulfate on the preexcitation phenomenon was tested. Except for an increase in pulse rate, there was no significant change.

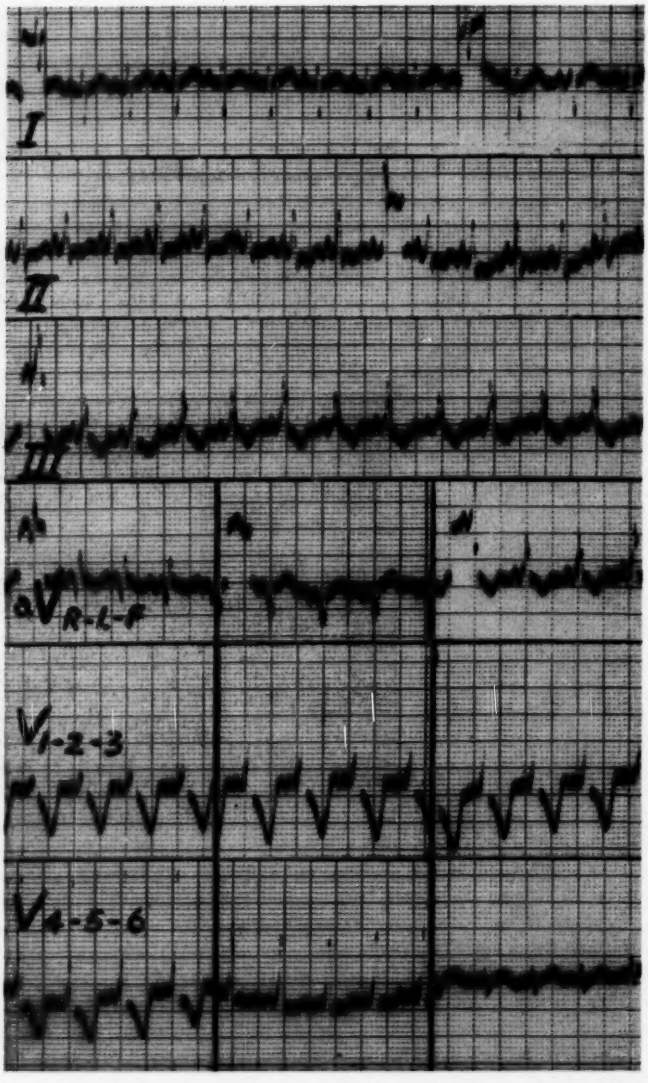

Fig. 1 (Case 1).—Electrocardiogram at age of 6 days showing Wolff-Parkinson-White syndrome: sinus rhythm, rate 175 per minute; P-R interval 0.07 second; QRS duration 0.09 second, and right axis deviation. Note slurring of upstroke of R wave in Leads II and III and notching of R wave in Lead III. Multiple unipolar precordial leads show in V_{1-3} unusually tall R waves (over the top of the record), depressed S-T segments, and deeply inverted T waves. Transitional RS complex and positive T wave in Lead V_6.

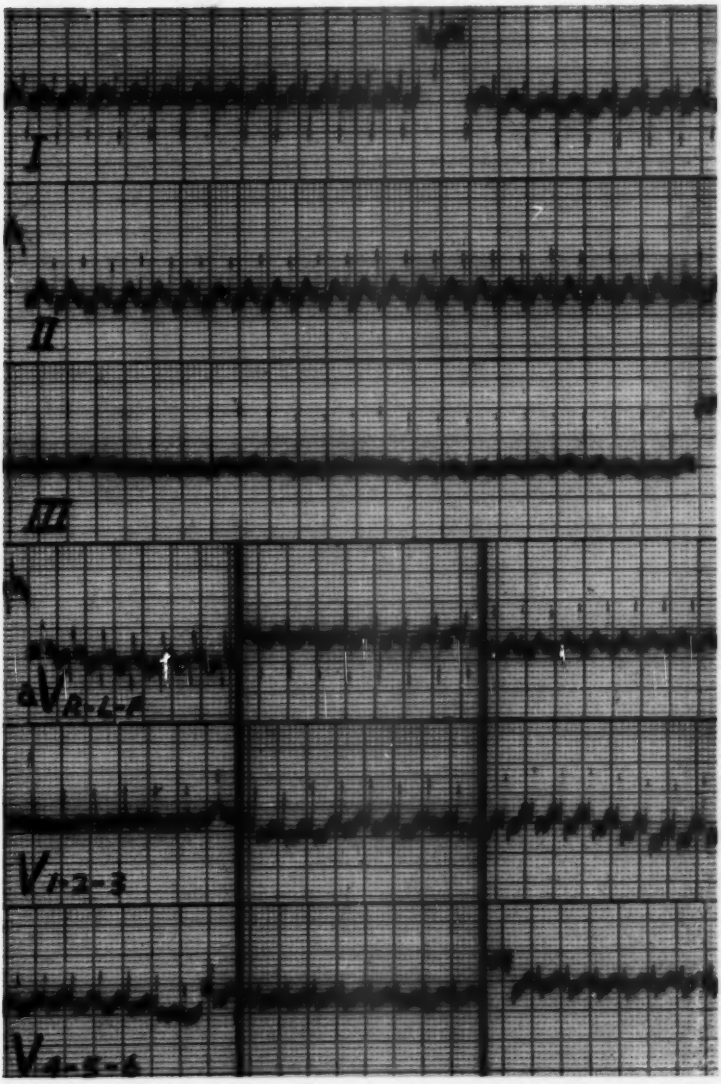

Fig. 2 (Case 1).—Electrocardiogram at 8 days showing paroxysmal supraventricular tachycardia: rate 295 per minute; QRS 0.04 second in duration and normal in form; P and T waves superimposed; right axis deviation. V leads at half standardization.

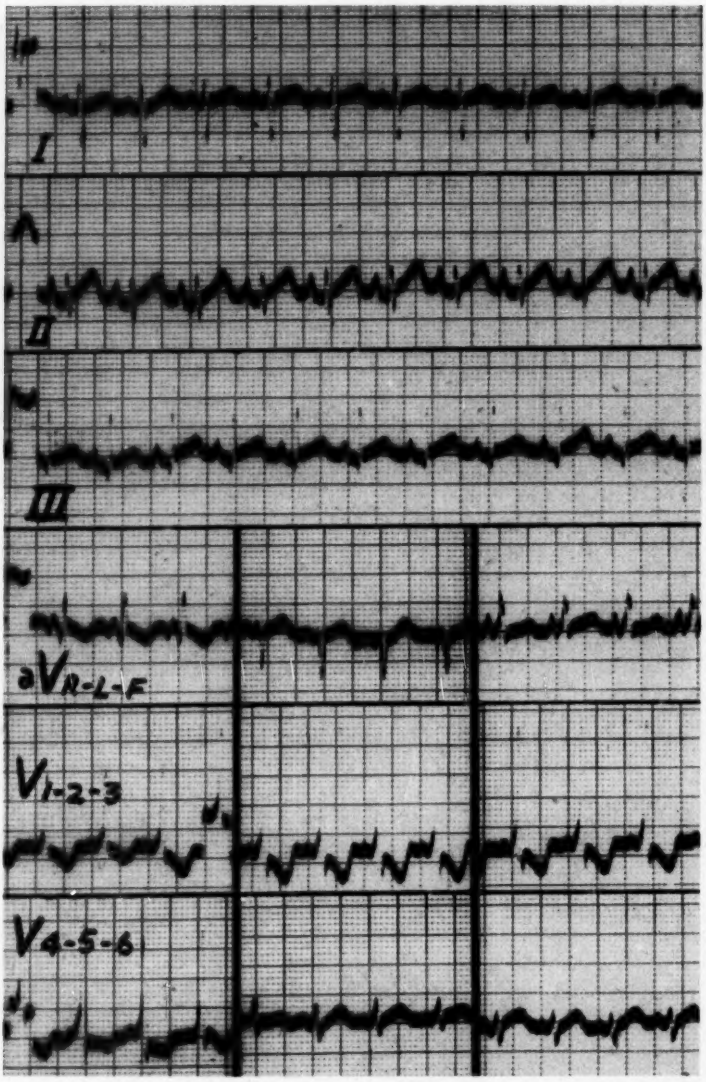

Fig. 3 (Case 1).—Electrocardiogram taken four hours after Figure 2. Normal sinus rhythm has returned spontaneously; rate 132 per minute; P-R 0.11 second, and QRS 0.04 second in Leads I to III, aV_R and aV_L. In aV_F and V_{1-6} Wolff-Parkinson-White syndrome has reappeared, as in Figure 1, with short P-R and prolonged QRS. P wave in Lead II is high and peaked.

Subsequent Course.—As she has grown older, the attacks of paroxysmal rapid heart action have decreased in frequency. She was readmitted to the hospital at the age of 2½ years because of paroxysmal supraventricular tachycardia following anesthesia for a tonsillectomy and adenoidectomy, and again at 5 years. The first attack reverted to normal rhythm after 0.1 gm. of digitalis was given; the second was stopped by supraorbital pressure. Since the age of 5 years, she has had no further attacks, and several electrocardiograms have shown normal conduction times and complexes (Fig. 4*C*). Her private physician [9] has observed the presence of a systolic murmur but has found no cardiac enlargement either clinically or by fluoroscopy. Her general health is excellent.

Case 3.—J. O. was born in the New York Hospital on June 27, 1935. In the nursery no cardiac murmurs or other abnormalities were detected. He was next seen at the age of 10 years because of the sudden onset, while playing ball, of marked fatigue, poor color, and

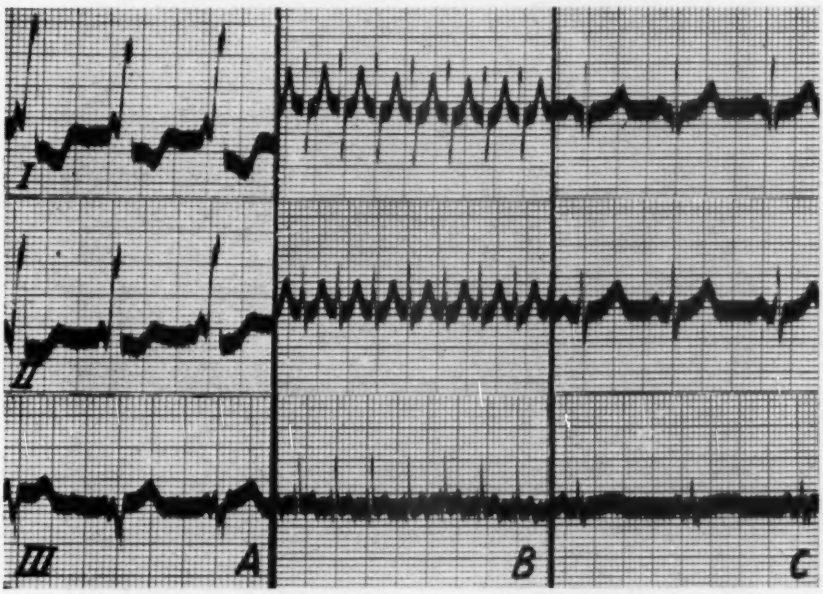

Fig. 4 (Case 2).—*A*, Wolff-Parkinson-White syndrome: sinus rhythm, rate 100 per minute; P-R 0.07 second; QRS 0.10 second; left axis deviation; QRS slurred on upstroke and notched, ST segments depressed in Leads I and II, and T_1 inverted. *B*, paroxysmal supraventricular tachycardia: rate 280 per minute; QRS 0.05 second, P and T waves superimposed, and electrical axis 90 degrees. *C*, normal tracing: rate 97 per minute; P-R 0.12 second, and QRS 0.04 second, no axis deviation, and electrocardiogram waves normal.

drowsiness. After a short sleep he awoke nauseated, he vomited once, and the symptoms disappeared.

His past history was remarkable only in that the mother was told when he entered school that he had a heart murmur. Nevertheless, he was able to play strenuously without undue fatigue, dyspnea, or cyanosis.

Physical Examination.—His temperature was 36.5 C. (97.7 F); pulse rate, 83; respiration, 18; blood pressure, 120/78 mm. of Hg in the arm and 140/80 in the leg, and weight, 47.5 kg. He was exceptionally well developed and well nourished. There was no cyanosis or clubbing, no precordial bulge or thrill. In the second and third left interspaces a harsh, short systolic

9. This follow-up has been done by Dr. Arthur Anderson, under whose care the patient has remained from the age of 15 months to her present age of 11 years.

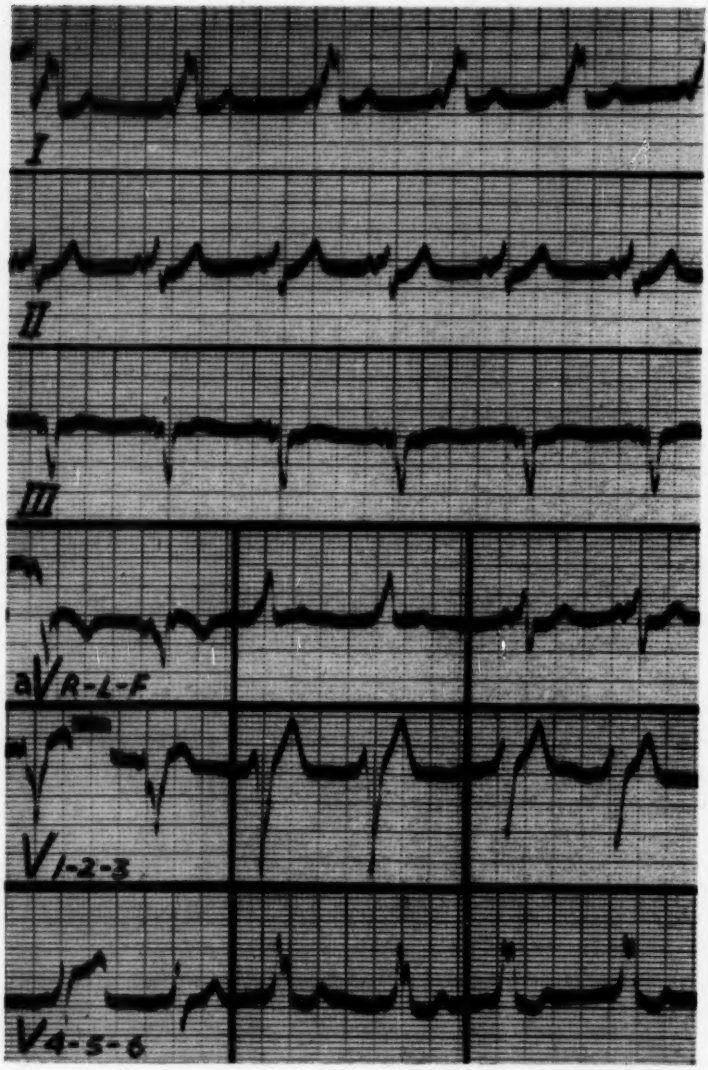

Fig. 5 (Case 3).—Wolff-Parkinson-White syndrome: rate 73 per minute; P-R 0.08 second; QRS 0.18 second, and left axis deviation. Note slurring of upstroke of R waves and notching of QRS complexes. T waves normal in limb leads but abnormal in precordial leads (diphasic in V_5 and $_6$, positive in V_{1-4}). V leads at half standardization.

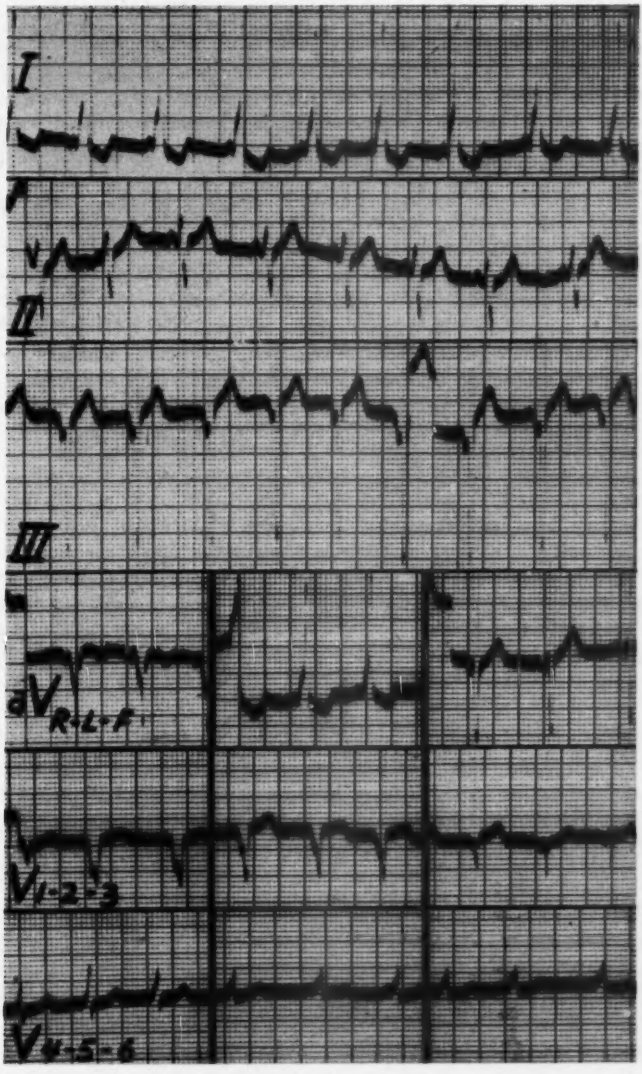

Fig. 6 (Case 4).—Wolff-Parkinson-White syndrome: rate 100 per minute; P-R 0.07 second; QRS 0.10 second, and left axis deviation. Slurring of initial stroke of QRS complex. T_1 diphasic (— +). V leads at half standardization.

murmur was heard. P_2 was accentuated; M_1 was split. With exercise the pulse increased from 90 to 140 and promptly returned to 90 per minute. The lungs were clear, the liver was not enlarged, and the findings on the remainder of the examination were within normal limits.

Laboratory Studies.—An electrocardiogram revealed a Wolff-Parkinson-White syndrome (Fig. 5). Fluoroscopy of the chest in the anteroposterior view showed a slightly enlarged heart with a prominent main pulmonary artery and large right and left pulmonary arteries, which exhibited expansile pulsations. In the left anterior-oblique view both the right ventricle anteriorly and the left ventricle posteriorly appeared enlarged. Barium swallow disclosed no left auricular enlargement. There was a left aortic arch and descending aorta. A roentgenogram of the chest confirmed the presence of slight cardiac enlargement. Vital capacity, sedimentation rate, and urinalysis were normal.

Course.—All electrocardiograms on his periodic examinations during the last five years have shown the Wolff-Parkinson-White syndrome. The systolic murmur and fluoroscopic evidences of slight cardiac enlargement have persisted. He has continued to exercise actively; however, in the past two years he has complained of exertional dyspnea and of tiring more quickly than others his age. He has had only two episodes which suggest paroxysmal tachycardia.

CASE 4.—J. Y. was first seen on March 20, 1950, at the age of 3½ years, because of recurrent brief episodes of fever associated with abdominal pain and nausea.

Physical Examination.—Her temperature was 37 C. (98.6 F); pulse rate, 105; respiration, 18, and weight, 16.8 kg. She was a well developed and well nourished Negro girl. There was no cardiac enlargement or palpable thrill. The heart sounds were regular. Over the right upper chest a venous hum was heard, and at the second left interspace there was a soft systolic murmur, which disappeared as the child sat up. Except for evidence of an upper respiratory infection, results of the remainder of the examination were unremarkable.

Laboratory Studies.—An electrocardiogram revealed a Wolff-Parkinson-White syndrome (Fig. 6). Fluoroscopy of the heart in the anteroposterior and the oblique views, with barium swallow, was normal. The blood count, urinalysis, Mazzini test, and tuberculin test were negative.

Course.—On her subsequent visits to the clinic all electrocardiograms have shown the Wolff-Parkinson-White syndrome. She has continued to have attacks of abdominal pain and fever; however, she has not been seen at the hospital during such an episode.

COMMENT

The finding of the Wolff-Parkinson-White syndrome at 6 days of age in the first baby, whose symptoms began on the first day of life, and the occurrence of episodes of tachycardia from birth in the second patient strongly suggest that the condition is of congenital origin. Reports in the literature of six other infants one month of age or less [5] with this syndrome, and with symptoms of paroxysmal tachycardia within the first week of life in at least two [10] of them, further support the congenital nature of the preexcitation syndrome.

It is generally agreed that the most likely explanation of the short P-R-prolonged QRS electrocardiogram is the presence of an accessory atrioventricular conducting pathway, which permits the premature depolarization of a portion of the ventricular muscle. This concept was originally suggested by Holtzmann and Scherf [11] and by Wolferth and Wood.[12] Later the hypothesis was confirmed by the histologic demon-

10. Footnote 2 *a* and *b*.

11. Holtzmann, M., and Scherf, D.: Über Elektrocardiogramme mit verkürtzer Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. klin. Med. **121**:404, 1932.

12. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), Am. Heart J. **8**:297, 1933.

stration of such pathways in patients with the Wolff-Parkinson-White syndrome, first by Wood, Wolferth, and Geckeler,[2w] and shortly afterward by Öhnell.[2m] Aberrant bundles have been found in a one-month-old infant, who during life displayed the Wolff-Parkinson-White syndrome, and who died in an episode of paroxysmal tachycardia.[2g]

That these accessory bundles of conducting tissue may arise as developmental anomalies is clear from Mall's studies on the embryology of the human heart.[13] In addition to the atrioventricular muscle, which is the chief muscle connection, he described in embryos from 13 to 21 mm. extra muscular connections between the auricles and ventricles. He related these observations to Kent's findings in animals of accessory conducting bundles.[14]

Although it is probable that the condition is congenital in origin, it is usually the only cardiac anomaly in the patient. The frequent occurrence of this syndrome in adults whose hearts are otherwise normal has long been known,[1] and in the reported infants and children there was usually no other evidence of heart disease.

The incidence of short-P-R-prolonged-QRS pattern in infants and children is difficult to ascertain. As Mannheimer [2e] has pointed out, the syndrome in infants may be missed if there is strict adherence to the figure of 0.10 second or greater as indication of prolongation of the QRS time. The QRS duration in infants (0.04 to 0.05 second) is normally shorter than in the older child or adult and may be prolonged when it measures 0.08 or 0.09 second. This is well illustrated in Case 1 of this report.

The numerous studies of the electrocardiogram in normal infants and children may shed light on the incidence of the Wolff-Parkinson-White syndrome. In a recent study at the New York Hospital [15] of the electrocardiograms of 175 normal babies at birth and on discharge from the newborn nursery and of an additional 400 normal children from 1 week to 14 years of age, no instances of preexcitation were found. No examples were reported in the 679 children between 6 months and 9 years of age who were studied by Maroney and Rantz [16] or in the 321 normal infants and children examined by Kushkin and Brockman.[17] Among the 260 children followed with serial tracings for an average of five years by Epstein,[18] no preexcitation electrocardiograms were described. A compilation of data on 1,500 additional normal infants and children studied in groups of 100 or more by a large number of investigators [19] failed to reveal any electrocardiograms with the Wolff-Parkinson-

13. Mall, F. P.: On the Development of the Human Heart, Am. J. Anat. **13**:249, 1912.

14. Kent, A. F. S.: The Right Lateral Auriculo-Ventricular Junction of the Heart, Proc. Physiol. Soc. London **48**:22, 1914.

15. Engle, M. A.: To be published.

16. Maroney, M., and Rantz, L. A.: Electrocardiogram in 679 Healthy Infants and Children, Pediatrics **5**:369, 1950.

17. Kushkin, L., and Brockman, L.: The Direction of the Precordial T Wave in 321 Normal Infants and Children, Am. J. M. Sc. **218**:65, 1949.

18. Epstein, N.: The Heart in Normal Infants and Children: Incidence of Precordial Systolic Murmurs and Fluoroscopic and Electrocardiographic Studies, J. Pediat. **32**:39, 1948.

19. Mannheimer, E.: Calibrated Phonocardiography and Electrocardiography: A Clinical-Statistical Study of Normal Children and Children with Congenital Heart Disease, Acta pædiat. (Supp. 2) **28**:1, 1940. Lincoln, E. M., and Nicolson, G. H. B.: Hearts of Normal Children, Am. J. Dis. Child. **35**:1001, 1928. Shookhoff, C., and Taran, L. M.: Electrocardiographic Studies in Infectious Diseases: I. Normal Children, Am. J. Dis Child. **42**:342, 1931. Burnett, C. T., and

(Footnote continued on next page)

White syndrome. Thus, in this composite group of over 3,400 normal infants and children there were no instances of short P-R-prolonged-QRS pattern. Ziegler's recent monograph, which described his electrocardiographic studies of 550 normal infants and children from birth to 16 years, included one probable example in a 4½-year-old boy and the classical picture in a 16-year-old girl. In Landtman's study [2d] of the electrocardiograms of 5,600 children under the age of 16 years, both with and without heart disease, there were only 2 with this abnormality, an incidence of 0.04%. It is estimated that the incidence in adults is 0.056 to 0.1%.[2m]

In almost all the reported cases of the Wolff-Parkinson-White syndrome in children the abnormality was detected because of the occurrence of paroxysmal tachycardia. Most of the attacks were of supraventricular origin; however, one 13-year-old boy was found to have paroxysmal ventricular tachycardia.[2x] Particularly in infants with the Wolff-Parkinson-White syndrome these attacks of tachycardia constitute a real risk. Two [20] of the six infants one month of age or less died as the results of attacks of tachycardia.

Although the symptoms of paroxysmal tachycardia in infancy are characteristic, they are also nonspecific, and the baby's true difficulty may be recognized and treated too late. The abnormally rapid heart rate, which is the clue to the diagnosis, may be overlooked or misinterpreted. Typically, an attack is associated with vomiting, irritability, an ashen-gray color, and a prostrate appearance. If the attack continues, signs of cardiac failure appear. The infant has rapid, difficult respirations and a cough. The temperature usually rises, but may be subnormal. Examination at this time reveals, in addition to the tachycardia, an enlarged heart, rales in the lungs, and hepatomegaly. Later, peripheral edema and ascites occur, and the baby may die in congestive failure or in peripheral vascular collapse.

In the treatment of an infant during an attack, digitalis, or one of its allied compounds, is quite effective and is considered by Hubbard,[21] Gibson,[22] and others [3] to be the drug of choice. Recurrent attacks of tachycardia may be reduced in frequency or even eliminated by maintaining the child on digitalis for a period of months or years. An adequate digitalizing dose for most infants is 35 mg. per kilogram of body weight of digitalis or 0.035 mg. per kilogram of body weight or digitoxin ("digitalline nativelle"), usually given in divided doses over a 12- or 24-hour period. The daily maintenance dose is between 0.1 and 0.2 of the total digitalizing dose. Quinidine sulfate is frequently beneficial in terminating an attack; however,

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Taylor, E. L.: Electrocardiograms on 167 Average Healthy Infants and Children, Am. Heart J. **11**:185, 1936. Perry, C. B.: The Electrocardiogram of Normal School Children, Arch. Dis. Childhood **6**:259, 1931. Reynolds, R. W.: T Wave Contour in the Precordial Leads During Childhood, Pediatrics **7**:400, 1951. Yu, P. N. G.; Joos, H. A., and Katsampes, C. P.: Unipolar Electrocardiogram in Normal Infants and Children, Am. Heart J. **41**:91, 1951. Seham, M., and Moss, A. J.: Electrocardiography in Pediatrics, Arch. Pediat. **59**:419, and 525, 1942. Hafkesbring, E. M.; Drawe, C. E., and Ashman, R.: Children's Electrocardiograms: I. Measurements for 100 Normal Children, Am. J. Dis. Child. **53**:1457, 1937. Richman, B., and Master, A. M.: The Unipolar Chest and Extremity Lead Electrocardiogram in Children (Newborn to 10 Years Old), Am. Heart J. **41**:687, 1951. Tudberg, P. B., and Atkinson, D. W.: Electrocardiograms of 100 Normal Infants and Young Children, J. Pediat. **36**:466, 1950.

20. Footnote 2*a* and *g*.

21. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687, 1941.

22. Gibson, S.: Supraventricular Paroxysmal Tachycardia in Infants and Children, M. Clin. North America **34**:217, 1950.

for small infants the optimal dosage schedule of this drug has not been determined. In desperately ill infants, immediate reversal of an attack may be accomplished by the administration of acetylcholine bromide in small doses. By intravenous administration 1 mg. may be given initially and the dose doubled every 10 to 15 minutes until conversion of the abnormal rhythm is obtained.[21] Atropine in a syringe should be available if needed as an antidote. Procaine amide ("pronestyl") hydrochloride, neostigmine methylsulfate, and phenylephrine neo-synephrine® hydrochloride may be useful.

In children the attacks of paroxysmal tachycardia are less hazardous than in infants. The paroxysms often can be stopped by the child's holding his breath, gagging, vomiting, or assuming a particular position. Supraorbital or carotid sinus pressure is frequently effective. In addition to these simpler measures, any of the drugs mentioned above may be used.

SUMMARY

Data on four children with the Wolff-Parkinson-White syndrome were presented. At the time the electrocardiographic abnormality was first detected, their ages ranged from 6 days to 10 years. In two of the patients episodes of paroxysmal tachycardia began in the first few days of life. Attacks of paroxysmal rapid heart action in young infants with this syndrome may be serious. Their recognition and treatment are discussed.

TRUNCUS ARTERIOSUS ASSOCIATED WITH A SINGLE VENTRICLE

JOHN L. SIDDOWAY Jr., M.D.
SALT LAKE CITY
AND
LIEUTENANT (jg) STANLEY M. CHERNISH (MC), U.S.N.R.

WITH THE advancement of cardiac surgery accurate diagnosis of congenital heart and vascular defects, by necessity, has had to keep pace. Not only is it important to determine which patients will be benefited by surgery, but those patients who will not be benefited must be recognized as well. Cardiac catheterization and angiocardiography have added much to the diagnostic armamentarium, but these techniques are difficult or impossible to use with small infants. The cyanotic infant still constitutes a difficult diagnostic problem, and many do not live to be over one month of age.

In the hope of facilitating a more complete understanding of the congenital heart disease which manifests itself in the first few months of life, we should like to report three unusual cases and a review of the literature of cases of persistent truncus arteriosus communis associated with a single ventricle.

Wilson,[1] in 1798, reported one of the first cases of congenital heart disease in the English literature. The abnormality consisted of a heart with a single ventricle and a persistent truncus arteriosus. Both these anomalies are rare, and the association of the two in one case is particularly so. A review of the literature shows that 15 possible cases of such an anomaly have been reported since then. These cases show many similarities, both clinically and pathologically, which have not been brought to light, since they have not been reviewed together in one group before. Previously some have been reviewed in connection with cases of cor biloculare and cor triloculare, or truncus arteriosus.

CRITERIA FOR DIAGNOSIS

It is beyond the scope of this paper to review the embryological development of the heart, but it is necessary to cite the criteria for the pathological diagnosis of persistent truncus arteriosus communis. This vessel is the single outlet of the heart; it passes cephalad, giving off both pulmonary and systemic circulatory systems. In normal development of the heart the embryonic bulbus and truncus arteriosus communis make over a 180-degree torsion and are divided into two portions, pulmonary and aortic, by a longitudinal septum. In the case of a true persistent truncus arteriosus communis the septum fails to complete its development to the

From the Department of Pediatrics, Gallinger Municipal Hospital and George Washington University School of Medicine.

1. Wilson, J.: A Description of a Very Unusual Formation of the Human Heart, Phil. Tr. Roy. Soc. London **18**:332-337, 1798.

base of the heart, leaving a single great vessel for a variable length and functioning as both pulmonary artery and aorta. In some cases, however, it is extremely difficult to be sure that the truncus arteriosus communis did not completely divide into the pulmonary and aortic portions with one of these embryonic vessels failing to develop. In such cases there usually remains an atretic vessel or cord, but there may be complete disintegration with no evidence of a second vessel leaving the heart. The remaining vessel, in these cases, is forced to take over the function of both the pulmonary artery and the aorta to preserve life and may give the appearance of a persistent truncus arteriosus communis. If the aortic portion fails to develop after the truncus arteriosus communis divides, the diagnosis of solitary pulmonary trunk is made. Humphreys [2] sets forth the following criteria: This vessel must have three semilunar cusps, contain no coronary ostia, give off the pulmonary circulation at the usual level, and continue on to form the aortic arch by the ductus arteriosus. The large vessels at the arch appear crowded. The atretic aorta often appears as a single coronary vessel, given off from the main vessel or from other large branches, and extends down to the heart, where it divides.

A solitary aortic trunk occurs when the pulmonary artery fails to develop after the division of the early truncus communis. There may be an atretic pulmonary artery or no evidence of such a vessel. The pulmonary blood supply comes from the ductus arteriosus or from a collateral bronchial vessel. In cases in which the pulmonary circulation is through the bronchial vessel it may be impossible to determine whether the sixth primitive aortic arch, which normally gives rise to the pulmonary artery, failed to develop from the undivided truncus or whether there was complete disintegration of the early-formed pulmonary arterial supply after division occurred. The ductus arteriosus develops from the embryonic left sixth aortic arch, and the assumption is made that if the pulmonary blood supply is through this vessel it is because the truncus communis has divided and the proximal portion of the pulmonary artery has disintegrated, forcing the ductus arteriosus to remain open to supply the lungs.

Humphreys [2] has set down eight criteria for anatomical diagnosis of persistent truncus arteriosus communis, but only two of these criteria are upheld by present-day authors (Taussig,[3] Lev and Saphir,[4] Collet and Edwards,[5] and MacGilpin [6]). 1. One abnormally large vessel leaves the heart without evidence of the second atretic vessel. 2. This vessel must give rise to both the systemic and the pulmonary circulations, and the coronary arteries must arise from the base. Shapiro,[7] in agree-

2. Humphreys, E. M.: Truncus Arteriosus Communis Persistens: Criteria for Identification of Common Arterial Trunk, with Report of Case with Four Semilunar Cusps, Arch. Path. **14**:671-700, 1932.

3. Taussig, H. B.: Clinical and Pathological Findings in Case of Truncus Arteriosus in Infancy, Am. J. Med. **2**:26-34, 1947.

4. Lev, M., and Saphir, O.: Truncus Arteriosus Communis Persistens, J. Pediat. **20**:74-88, 1942.

5. Collet, R. W., and Edwards, J. E.: Persistent Truncus Arteriosus, S. Clin. North America **29**:1245-1270, 1949.

6. MacGilpin, H. H., Jr.: Truncus Arteriosus Communis Persistens, Am. Heart J. **39**:615-625, 1950.

7. Shapiro, P. F.: Detorsion Defects in Congenital Cardiac Anomalies: Report of 3 Cases, with Analysis of Mechanism of Their Formation, Arch. Path. **9**:54-68, 1930.

ment with Humphreys, states that a true persistent truncus arteriosus communis must have four cusps and that only two cases of such an anomaly have been reported (Preisz and Santa Cruz). In neither case was it associated with a heart with a single ventricle. Taussig [8] takes a practical point of view and does not differentiate these three conditions. She considers them all in one group as truncus arteriosus.

REVIEW OF LITERATURE

In reviewing the literature on truncus arteriosus associated with a single ventricle, we have found 25 cases treated by the authors as instances of true truncus arteriosus, but in our opinion nine should be classified as solitary pulmonary or aortic truncus (these are all contained in the accompanying Tables). In addition, five cases of solitary pulmonary truncus and five cases of solitary aortic truncus which presented atretic vessels, and obviously not persistent truncus arteriosus, have been reviewed. Although they are not included in the Tables, they will be discussed later.

In the six cases in which solitary pulmonary truncus was thought to be present, the coronary arteries are described as taking their derivation from the truncus above the base or from one of the great vessels from the aortic arch. Along with other criteria already cited, such a coronary artery would, of necessity, be an atretic aorta, carrying blood in a retrograde manner to supply the cardiac muscle. In the three cases in which solitary aortic truncus was thought to be present, the pulmonary circulation was derived from the ductus arteriosus.

In the rest of the cases, those in which the condition was considered to be true persistent truncus arteriosus communis, the pulmonary circulation was given off directly from the truncus; however, the coronary circulation was described in only 2 of the 16 cases. If the coronary circulation were known, some of these cases, and possibly all, might have to be considered as cases of solitary pulmonary truncus. They are left under the classification of truncus arteriosus because they have been considered as such in the past. Regardless of the pathological classification, in each case only one functional vessel leaves the heart and has the common purpose of giving rise to the coronary, pulmonary, and systemic blood supply (Fig. 1).

Conn, Clark, and Kissane [9] state that 77 cases of cor triloculare have been reported up to 1950. In 22 cases there were two ventricles, and in 55 there were two atria. In no case of any of the three types of truncus was the anomaly associated with the biventricular type. On the other hand, in at least 18 cases a persistent truncus was associated with the biatrial type. Lightner [10] and Shapiro [7] were the only ones to describe cases in which any evidence of a septum or a rudimentary fourth chamber was noted. Conn, Clark, and Kissane [11] further state that 49 cases

8. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

9. Conn, J. J.; Clark, T. E., and Kissane, R. W.: Cor Biloculare: Report of 4 Cases, Am. J. Med. **8**:180-186, 1950.

10. Lightner, C. M.: Unusual Congenital Malformation of the Heart: Cor Biloculare, with Ostium Atrioventricular Commune, Pulmonary Atresia, Displacement of Right Pulmonary Veins and Associated Somatic Defects, J. Tech. Methods **19**:148-155, 1939.

11. Conn, J. J.; Clark, T. E., and Kissane, R. W.: Cor Triloculare: Report of 4 Cases, Am. J. Med. **8**:187-195, 1950.

of cor biloculare have been reported. Seventeen cases of "truncus" were found to be associated with this condition. We considered two atria to be present when there was a second appendage receiving the pulmonary veins, as in only 2 of the 35 cases studied was an atrioventricular valve found in the left atrium.

The Tables are a brief summary of 25 cases found in the literature [12] in which we believe the anomaly might fit the pathological diagnosis of persistent truncus arteriosus most closely.

COMMENT

It will be seen from the Tables that these 25 cases so closely resemble each other that it would be impractical to comment on them except as a single group. The average age at death was 17½ days, the patients ranging from one stillbirth to a 5-month-old infant, and most deaths occurred within 2 to 10 days after birth. The

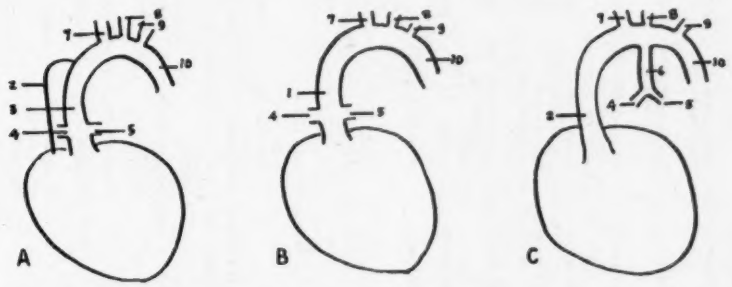

Fig. 1.—*A*, solitary pulmonary trunk; *B*, persistent truncus arteriosus; *C*, solitary aortic trunk. *1* indicates persistent truncus arteriosus; *2*, aorta; *3*, common pulmonary artery; *4*, right pulmonary artery; *5*, left pulmonary artery; *6*, ductus arteriosus; *7*, innominate artery; *8*, left common carotid artery; *9*, left subclavian artery, and *10*, descending aorta.

12. (*a*) Wenner.[14] (*b*) Mannheimer, E., and Nordenfelt, P. J.: Four Cases of Congenital Cardiac Disease, Acta paediat. **23**:200-221, 1938. (*c*) Bradley, S. M.: Tricoelian Human Heart, Brit. M. J. **1**:33-34, 1873. (*d*) Deutsch: Über Cyanosis; abstracted, Schmidts Jahrb. **71**:454-456, 1851. (*e*) Woods, R. H., and Williams, G. A.: Primitive Human Hearts, Am. J. M. Sc. **175**:242-255, 1928. (*f*) Potts, R.: Ein Beitrag zu den Bildungsfehlern und foetalen Erkrankungen des Herzens, Jahrb. Kinderh. **13**:11-34, 1879. (*g*) Rizzi, I.: Contributo allo studio di varie malformazioni cardiache, Gior. clin. med. **19**:863-882, 1938. (*h*) Krausse, O.: Ein Beitrag zur Lehre von den kongenitalen Herzfehlern und ehrer Komzidenz mit andern Missbildungen, Jahrb. Kinderh. **62**:35-49, 1905. (*i*) Mehta and Hewlett.[13] (*j*) Clark, E.: Malformation of Heart, Tr. Path. Soc. London **36**:178, 1885. (*k*) Giustra, F. X., and Tosti, V. G.: True Cor Biloculare in Identical Twins, Am. Heart J. **17**:249-250, 1939. (*l*) Michelson, R. P.: Report of a Case of Cor Biloculare with Persistent Truncus Arteriosus, ibid. **25**:112-115, 1943. (*m*) Dagnini, G.: Due casi di tronco arterioso commune persistente, Clin. pædiat. **13**:601-614, 1931. (*n*) Wilson.[1] (*o*) Conn and others.[9] (*p*) Popjak, G.: Two Cases of Congenital Cardiac Disease, J. Path. & Bact. **54**:67-73, 1942. (*q*) Standert, H. C.: Phil. Tr. Royal Soc. London **95**:228, 1805. (*r*) Rathbotham: The Heart of an Infant Consisting of Only One Auricle and Ventricle, Tr. Path. Soc. London **1**:48, 1846-1848. (*s*) Forester, J. C.: A Heart Consisting of Only Two Cavities, ibid. **1**:48-49, 1846-1848. (*t*) Farre, J. R.: Pathological Researches: Essay I, On Malformations of the Heart, London, 1814. (*u*) Oestreicher, D. L., and Harris, G. E.: Am. Heart J. **39**:626, 1950. (*v*) Vernon, H. H.: Angeborene Herzfehler, abstracted in Schmidts Jahrb. **96**:298-299, 1857. (*w*) Tow, A.: Cor Biloculare with Truncus Arteriosus and Endocarditis, Am. J. Dis. Child. **42**:1413-1416, 1931.

TABLE 1.—*Data on Cases of Truncus Arteriosus Communis Associated with Cor Triloculare Biatriatum*

Author	Age at Death	Cyanosis	Murmur	Heart Enlargement	Atria	Condition of the 1 Atrioventricular Valve	Pulmonary Artery	Coronary Artery
Wenner [14]	2½ days	No symptoms described	.....	Marked	Large right; rudimentary left	3 cusps	2 vessels from truncus	Right from posterior sinus of Valsalva
Mannheimer and Nordfelt [12b]	3 mo. 11 days	In spells	Systolic at 3 days	Marked	Large right; rudimentary left	3 cusps	1 vessel from truncus	Not described
Bradley [12c]	48 hr.	By 30th hr.	.....	No mention	Large right; rudimentary left	More mitral	.....	.....
Deutsch [12d]	45 min.	Bluish-gray	.....	None	Large right; small left	Large; 4 cusps not located	1 vessel from truncus	.....
Woods and Williams [12e]	3 days	By 60th hr.	Continuous	No mention	Large right; rudimentary left	2 cusps	1 vessel from innominate a.	Not described
Potts [12f]	20 min.	None	.....	Moderate	Large right; rudimentary left	2 large cusps; 1 small one	2 vessels from truncus	.....
Rizzi [12g]	1 mo.	In spells	.....	Generally	2 atria	Located between atria	1 vessel from truncus	.....
Krausse [12h]	9 days	From birth	.....	Moderate	2 well-developed	Large, knotty, and between atria	1 vessel from truncus	.....
Mehta and Hewlett * [13]	56 yr.	Whole life	Systolic	Moderate	Large right and left	Normal mitral and tricuspid *	From innominate a.	Normal
Clark [12j]	10 wk.	.....	.....	.....	2	In left atrium	1 vessel from truncus	.....

* Only case with two atrioventricular valves (normal tricuspid and mitral).

TABLE 2.—*Data on Cases of Truncus Arteriosus Associated with Cor Biloculare*

Author	Age at Death	Cyanosis	Murmurs	Condition of the 1 Atrioventricular Valve	Heart Enlargement	Atria	Pulmonary Artery	Aortic Cusps
Giustra and Tosti [12k] (Case 1) *	30 hr.	At 30 hr.	Systolic	Tricuspid	Moderate	1	2 vessels from truncus	3
(Case 2)	39 hr.	At 30 hr.	None	Tricuspid	Moderate	1	2 vessels from truncus	3
Michelson [12l]	3 days	On 2d day	None	Incomplete development	None	1	1 vessel from truncus	3
Dagnini [12m]	Stillborn	None	.....	Tricuspid	.....	1	2 vessels from truncus	3
Wilson [1]	7 days	.....	.....	Not described	.....	1	1 vessel from aorta	3
Conn [9]	42 hr.	38 hr.	.....	Moderate	.....	1	2 vessels from truncus	3

TABLE 3.—*Data on Cases of Probable Aorta Solitaris Associated with Single Ventricle*

Author	Age at Death	Cyanosis	Murmurs	Condition of the 1 Atrioventricular Valve	Heart Enlargement	Atria	Pulmonary Artery	Aortic Cusps
Popjak [12p]	21 hr.	At 5 hr.	.....	4 cusps	Considerable	1	From ductus arteriosus	3
Standert [12q]	10 days	From birth	.....	Tendinous valves	Not mentioned	1	From ductus arteriosus	..
Rathbotham [12r]	10 days	From birth	.....	Tendinous valves	Not mentioned	1	From ductus arteriosus	..

TABLE 4.—*Data on Cases of Solitary Pulmonary Truncus*

Author	Age at Death	Cyanosis	Heart Enlargement	Atria	Condition of the 1 Atrioventricular Valve	Pulmonary Artery	Coronary Artery	Pulmonary Cusps
Forester [12s]	72 hr.	Developed	Moderate	1	Large	2 vessels from truncus	From aortic arch	3
Farre [12t]	79 hr.	After 40 hr.	Moderate	Large right; rudimentary left	Tricuspid in atria	2 vessels from truncus	From common brachiocephalic artery	..
Oestreicher and Harris [12u] (Case 1)	5 days	Only on 5th day	Moderate	Small left and right	Tricuspid	2 vessels from truncus	From common brachiocephalic artery	3
(Case 2)	3 days	On 3d day	Moderate	Small left and right	Tricuspid	2 vessels from truncus	From common brachiocephalic artery	3
Vernon [12v]	8 days	None	Not described	Large right; small left	Bicuspid	2 vessels from truncus	From innominate artery	..
Tow [12w]	5 mo.	Always	Enormous	1	Bicuspid	2 vessels from truncus	From left pulmonary artery	..

one exception was the case of Mehta and Hewlett,[13] in which the patient lived 56 years. The presence and degree of cyanosis were variable, the cyanosis being absent in three cases and described as present at birth in only four cases. The average time of onset was 24 hours after birth, the age varying from birth to 5 days of age. Intensity of cyanosis was not well described but in most cases ranged from mild to moderate, with a few in which it was marked; four infants were not cyanotic. In 14 cases dyspnea was noted to be present terminally. The presence or absence of murmurs was noted in eight cases, as follows: Murmurs were absent in three, systolic in three, continuous in one, and "loud" in one.

Postmortem examination revealed the heart to be greatly enlarged in 4 cases, moderately enlarged in 11 cases, and not enlarged in 2 cases. In each case the interatrial septum was open by necessity, the communication varying from a slit to complete absence. In the 14 cases with two atria the findings were most interesting and typical. In 11 cases the right atrium was described as being much larger than the left, which was merely rudimentary and formed a small channel, through which blood passed to the right atrium. The flow of blood in such a direction was necessitated by the absence of a valve (mitral) between the left atrium and the single ventricle. In fact, in each case, with the exception of the one reported by Mehta and Hewlett,[13] there was only one valvular opening between the atria and the ventricle. Such a valve in the biatrial heart was located in the right atrium in 11 cases, between the atria in 2, and in the left atrium in 1. Location was poorly described in two cases. Of the total 25 cases, the single valve had three cusps in 12 cases, two cusps in 4 cases, and four cusps in 2 cases, and the number of cusps was not given in 4 cases.

As previously described, the pulmonary arteries were derived directly from the truncus in all but the three cases of solitary aortic trunk, in which the origin was from the ductus arteriosus. In 12 cases the two pulmonary arteries arose separately from the truncus arteriosus, and in 8 their origin was from a single trunk. In none of these 25 cases was an atretic pulmonary artery noted. The number of cusps in the truncus was given as three in all 12 cases in which the number was described. In all 11 cases in which the condition of the lungs was noted, congestion was present, being marked in most.

These cases, except for the case of Mehta and Hewlett,[13] resemble each other so closely that a hypothesized case might be described which would not be too divergent from any of the 25 cases. Such a case might be that of an infant who appeared normal until 36 hours of age, when he was noticed to become cyanotic with feedings. A murmur may or may not have been heard at this time; moderate cyanosis would soon have become constant but may have improved with administration of oxygen. Feedings would have been taken poorly. Dyspnea may or may not have developed on the third to the sixth day, and death would have occurred on the 4th to the 15th day of life. The heart would have been moderately enlarged and would have shown one of the three types of "truncus," in addition to a single ventricle. There would have been only one atrioventricular valve, tricuspid in nature, and if there were two atria, the right would have been much larger than the (rudimentary) left. The lungs would have been greatly congested (Fig. 2).

13. Mehta, J. B., and Hewlett, R. F. L.: Cor Triloculare Biauriculare, Brit. Heart J. **7**:41-44, 1945.

REPORT OF CASES

CASE 1.—This infant boy was born to a 28-year-old white mother who had had several episodes of uterine bleeding and hospitalizations during pregnancy. Delivery was normal, but the child weighed only 5 lb. 2 oz. (2,325 gm.). He was discharged as a normal infant from a maternity hospital at 10 days of age, weighing 5 lb. 4 oz. (2,381 gm.). His parents noted that his skin was always an olive color, that he breathed somewhat rapidly, and that he fed very slowly. He reached a maximum weight of 5 lb. 12 oz. (2,608 gm.) eight days before admission to Gallinger Municipal Hospital, when he was 28 days old. Examination at the time of admission revealed a small, pale, moderately cyanotic infant, who was respiring rapidly and appeared moribund. Grade-I to Grade-II systolic murmur, which was inconsistent in audibility, was heard over the left precordium. A posteroanterior x-ray of the chest showed the heart to be considerably enlarged and globular in shape and the lung field to be clear except for some congestion in the right hilar area. Oxygen did not improve the infant's color, and he died about 12 hours after admission, at the age of 29 days.

Pathological findings of significance were confined to the heart, which was moderately enlarged. The right atrium was much larger than the left (small) one, which received pulmonary veins but had no connection with the ventricle. The interatrial septum was open about 1 cm. The tricuspid valve was normal, and there was no evidence of a septum in the single ventricle. One large vessel left the superior center of the ventricle, giving off two

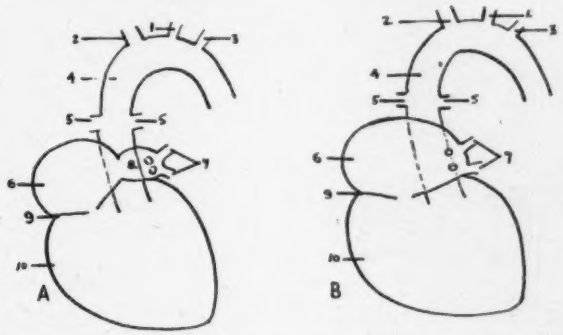

Fig. 2.—*A*, cor triloculare; *B*, cor biloculare. *1* indicates left common carotid artery; *2*, innominate artery; *3*, left subclavian artery; *4*, truncus arteriosus; *5*, pulmonary arteries; *6*, large right atrium; *7*, pulmonary veins; *8*, small rudimentary left atrium; *9*, single atrioventricular valve (tricuspid usually), and *10*, enlarged single ventricle.

pulmonary arteries and passing on as the normal aorta. A three-cusp valve guarded its opening, but no coronary ostia were found. Instead, the coronary vessels were found to originate from a very small vessel, 2 mm. in diameter, extending 2 cm. above the heart behind the pseudotruncus and lying free where it had been cut from its origin, which could not be found. This atretic vessel, first thought to be the coronary, must have been the atretic aorta.

CASE 2.—This full-term infant had a normal birth following a normal pregnancy and labor. He became cyanotic a short time after birth; his cry was feeble, and his respirations were rapid. A slight to moderate harsh, rough systolic murmur was heard along the left sternal border. The electrocardiogram presented a slight shift of axis to the right, a sinus rhythm with a rate of 150, and P-R interval of 0.12 second. The QRS complex in Leads V_1 and V_6 suggested right ventricular hypertrophy, but within the range of normal. T waves were upright in Leads 1, 2, and 3, down in Leads aVR and aVL, and upright in Lead aVF. X-ray and fluoroscopic studies demonstrated marked cardiac enlargement, which was more pronounced on the right side. The infant became more cyanotic and dyspneic and died at 63½ hours of age.

Pathological findings of significance were a large right and a rudimentary left atrium and a single ventricle; only one valve, the tricuspid, measuring 5 cm., was present between the ventricle and the right atrium. The small left atrium received the pulmonary veins but had

no connection with the rest of the heart except through the open interatrial septum. Only one large vessel with a three-cusp valve left the ventricle, taking the normal course and giving off the normal branches of the aorta. In addition, however, it gave rise to the two pulmonary arteries on its posterior surface. As in Case 1, the coronary arteries arose from an atretic aorta, 2 cm. in diameter, found behind the pseudotruncus. In the wall of the single ventricle at the base of the atretic aorta a very small second ventricle was found, measuring 1 by 1.5 cm.

These two cases were at first thought to be instances of truncus arteriosus associated with a single ventricle, but after a careful search the atretic aortas, and in Case 2 a second ventricle, were found. It is our opinion that the 14 cases considered

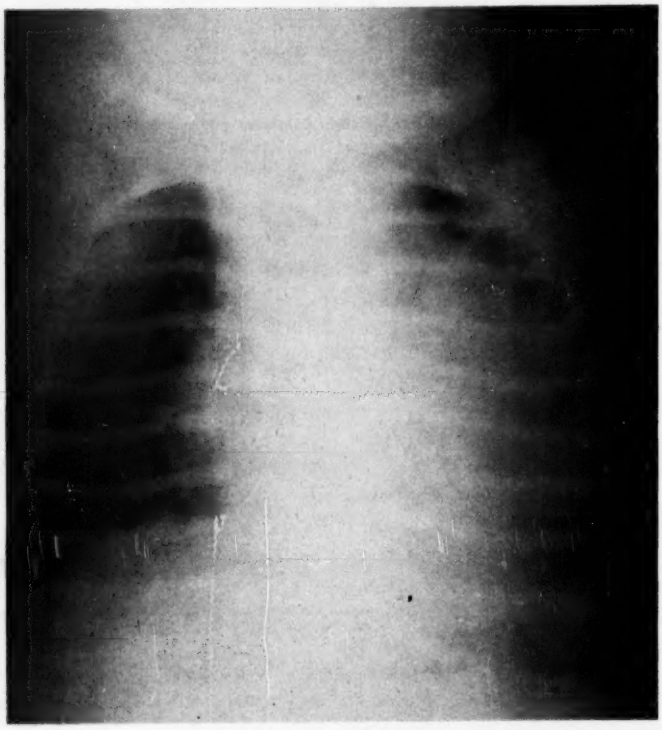

Fig. 3 (Case 2).—Posteroanterior roentgenogram.

to be instances of truncus arteriosus associated with a single ventricle, with no description of the coronary arteries, are in reality cases of pseudotruncus almost identical to these 2 cases. This leaves only three cases in the literature which meet the criteria for truncus arteriosus associated with a single ventricle (Wenner,[14] Mehta and Hewlett,[13] and Shapiro [7]).

Case 3.—This full-term Negro infant was born in Gallinger Municipal Hospital after a normal pregnancy and labor, which was facilitated by use of a Willett clamp for an hour. Except for a moderately loud, harsh systolic murmur heard along the left sternal border, the

14. Wenner, O.: Beiträge zur Lehre der Herzmissbildungen, Virchows Arch. path. Anat. **196**:127-168, 1909.

infant was normal, with a good cry, color, and activity. At 24 hours of age he began to have cyanotic attacks at feeding, and at 36 hours, he remained slightly cyanotic. Respirations were rapid and labored, and the liver was found to be 3 to 4 cm. below the costal margin. The patient was placed in oxygen, and cyanosis disappeared. Digitalization was rapidly completed. The x-ray revealed generalized enlargement of the heart with no specific configuration and clear lung fields. The electrocardiogram showed an R wave of 3 mm. and an S wave of 7 mm. in Lead 1. The R wave was 8 mm. in Lead 3, with no S wave. The T and P waves were normal, and unipolar limb leads were demonstrative of a vertical heart. Chest leads revealed a normal condition, except for hypertrophy of the right ventricle. The condition improved in the next three days, but the infant began to show cyanosis and dyspnea while in oxygen and died at 7 days of age.

Pathological findings of significance were confined to the heart, which presented a large, dilated right atrium and a small left atrium. The rudimentary left atrium had no atrioventricular valve but received the pulmonary veins and communicated with the rest of the heart through an interatrial septum defect 1 cm. in diameter. The tricuspid valve was normal, communicating with one very large ventricle, from which there was only one outlet, guarded by a three-cusp valve. This large vessel gave off the two pulmonary arteries and then continued cephalad as a slightly constricted portion, joining the aortic arch from beneath. At the arch the great vessels were crowded and the descending aorta was normal, but at the right extremity of the arch was a small vessel, 3 mm. in diameter, passing down to the heart behind the pseudotruncus. At the heart this small vessel gave rise to the coronary arteries and was found communicating with a very small rudimentary second ventricle, having no visible connection with the large right ventricle. The lungs were moderately congested.

The third case is obviously one of a solitary pulmonary truncus, because the atretic aorta is larger but differs essentially in no other way from that in the previous two cases.

Shechter and Meranze,[15] Rukstinat,[16] and Taussig [17] described cases very similar to Case 3, with the same characteristics and with death occurring at 23, 3, and 3 days of age respectively. Davies and MacConaill [18] and Conn and associates [9] described cases differing from Case 3 only in so far as they were cases of cor biloculare. The following authors described cases of solitary aortic truncus with an atretic pulmonary artery. In all the characteristics described above were present: Miskall and Frazer,[19] death at 3½ days; Lightner,[10] death at 6 months; Kugel,[20] death at 4 months; Rossman,[21] death at 9½ months, and Northrup,[22] death at one month. The first case is one of cor triloculare; the rest are cases of cor biloculare.

Shapiro [7] described a case in which the anomaly meets the criteria of true persistent truncus arteriosus associated with one large and one very rudimentary

15. Shechter, R. F., and Meranze, D. R.: Cor Biloculare: Report of a Case, J. Pediat. **25**:150-154, 1944.

16. Rukstinat, G. J.: Aortic Stenosis, Atresia and Adult Coarctation Associated with a Triloculate Heart, Arch. Path. **26**:102-106, 1938.

17. Taussig, H. B.: Clinical and Pathological Findings in Aortic Atresia, Bull. Johns Hopkins Hosp. **76**:75-82, 1945.

18. Davies, F., and MacConaill, M. A.: Cor Biloculare, with Note on Development of Pulmonary Veins, J. Anat. **71**:437-446, 1937.

19. Miskall, E. W., and Frazer, J. A.: Cor Biloculare: Report of a Case, Ohio M. J. **42**:369-370, 1946.

20. Kugel, M. A.: Congenital Heart Disease: Clinical and Pathological Study of 2 Cases of Truncus Solitarus Aorticus, Am. Heart J. **7**:262-273, 1932.

21. Rossman, J. I.: Cor Triloculare with Transposition of Great Cardiac Vessels and Atresia of Pulmonary Artery, Am. J. Clin. Path. **12**:534-542, 1942.

22. Northrup, W. P.: Proc. New York Path. Soc., p. 40, 1888.

ventricle and which would also fit in as a characteristic case. Only one of 36 cases reviewed did not fit the characteristics described—the case of Mehta and Hewlett.[13]

Furthermore, Friedman, Murphy, and Ash [23] described four cases which were like our Case 3 in almost every respect. In their cases the aorta was clearly evident, although atretic. In reviewing the literature they found 30 other cases which were similar to theirs. Death occurred in from 1 day to 25 days. In their opinion, the basic anomaly was atresia of the aorta with the resultant pronounced hypoplasia of the left ventricle, left atrium, and mitral valve, and a dilated right ventricle and pulmonary artery functioning as a truncus.

Since a careful search will reveal a second rudimentary ventricle in the muscular wall of most hearts with a single ventricle and, as demonstrated, the atretic aorta is easily overlooked, we do not believe the hearts in the cases reviewed by Friedman, Murphy, and Ash [23] differ essentially from those in the cases we have reviewed and reported, except for the solitary aortic trunks.

We propose that atresia or aplasia of the left atrioventricular valve is the basic malformation giving rise to the anomalous hearts under discussion. Without an opening from the left atrium into the left ventricle because of aplasia or pronounced congenital stenosis of the mitral valve, the left atrium functions only as a channel to escort the blood through an interatrial septum defect into the right atrium and right ventricle and out the pulmonary artery. Some blood is sent to the lungs, and the rest continues through the ductus arteriosus into the arch and descending aorta. The left ventricle and aorta are completely bypassed. As found in specimens, the left ventricle is a small cavity in the wall of the dilated right ventricle, and the aorta is a very small artery receiving blood from the aortic arch and carrying it in a retrograde manner to the heart muscle. The right side of the heart is dilated, and the left is extremely hypoplastic. In the eight cases of solitary aortic trunk associated with a single ventricle complete transposition of the great vessels would also have had to occur in addition to atresia of the mitral valve. This is borne out by the fact that a solitary pulmonary artery occurs much more frequently associated with a single ventricle than a solitary aorta.

A third hypothesis, that of simultaneous failure in the development of the ventricular and bulbotruncal septums, is necessary to explain the three probable cases of a true truncus arteriosus communis associated with a true single ventricle (Wenner,[14] Mehta and Hewlett,[13] and Shapiro [7]). It is probable that cases in which each of these explanations is applicable do occur.

The clinical outcome is the same no matter what the explanation may be. All patients do poorly and die in infancy. In all cases reviewed there appeared to be an adequate pulmonary blood supply, and the early death may have been due in part to what Rodgers and Edwards [24] call intrapulmonary pulmonary stenosis due to pulmonary hypertension resulting from a single-ventricle ejectile force, which sends blood to both the pulmonary and the systemic circulation. The lungs of most patients were markedly engorged, and there appeared to be some impediment to the return of blood by the rudimentary left atrium. None of the patients could have been benefited by the artificial shunts at present performed.

23. Friedman, S.; Murphy, L., and Ash, R.: Aortic Atresia with Hypoplasia of the Left Heart and Aortic Arch, J. Pediat. **38**:354-367, 1951.

24. Rodgers, H. M., and Edwards, J. B.: Cor Triloculare Biatriatum, Am. Heart J. **41**:299-310, 1951.

SUMMARY AND CONCLUSIONS

The congenital cardiac anomaly of true persistent truncus arteriosus communis associated with a single ventricle is a very rare condition and can be said to have occurred in only three cases. The cases reported as of such an anomaly are either not completely described or are identical with the three cases reported here, in which the anomaly consisted of a pseudotruncus arteriosus associated with a single functional ventricle and a small rudimentary second ventricular cavity. It is our opinion that these incompletely described cases are also identical with such an anomaly, as the description of the coronary arteries is the most important missing item.

There develops, however, a clinical course which is similar in all cases of a "truncus" associated with a "single ventricle" and characterized by a symptom-free period of a few hours to a few days, at which time the infant begins to eat poorly, to show mild to moderate cyanosis, and, finally, to become dyspneic, with death occurring in most cases before the 20th day of life. Some patients have lived as long as several months, and one patient died at the age of 56. The electrocardiogram usually shows some right-axis deviation but is not diagnostic, nor are the x-ray and fluoroscopic findings. The heart shows moderate to marked generalized enlargement, and the lung fields are congested. At postmortem examination the right atrium is seen to be greatly enlarged, and the left atrium is small and rudimentary and communicates with the rest of the heart through the interatrial septum defect, as the left atrioventricular valve is missing. The single functional ventricle is markedly dilated, and only one functioning vessel leaves the heart. In most cases it is proved to be the pulmonary artery functioning also as the aorta by evidence of a very atretic aorta leaving the heart and having the function of a coronary artery carrying blood in a retrograde manner from the aortic arch. In fewer cases,[8] the pseudotruncus is the aorta, also giving rise to the pulmonary blood supply, and the pulmonary artery is absent or atretic. It is postulated that the basic anomaly causing such pronounced distortion of the heart is the failure in the development of the mitral valve. In the cases in which the solitary aorta exists the transposition of the great vessels is also proposed.

Thirty-six cases are reviewed, and all but 1 share the characteristic features. Friedman, Murphy, and Ash [23] have reviewed 34 cases which clinically and, for the most part, anatomically do not differ from the cases we have reviewed; pathologically we have termed them cases of solitary pulmonary truncus associated with a single ventricle. We further believe that the association of a pseudotruncus with a functional single ventricle is not as rare as the literature would indicate and that more cases will be seen when the condition is looked for.

4678 Holladay Blvd. (Dr. Siddoway).

Dr. Bernard B. Walsh assisted in the preparation of the manuscript and granted us his permission to use Case 2. Dr. Gerhart Gordon and Dr. Matthew Marano assisted in the translations of the literature.

INFECTION AS CAUSE OF FOLIC ACID DEFICIENCY AND MEGALOBLASTIC ANEMIA

Experimental Induction of Megaloblastic Anemia by Turpentine Abscess

CHARLES D. MAY, M.D.
IOWA CITY
CHARLES T. STEWART, M.D.
AGNES HAMILTON, M.A.
AND
R. J. SALMON, M.Sc.
MINNEAPOLIS

A SURVEY of histories of infants with megaloblastic anemia reveals that infection and ascorbic acid deficiency are common features of possible etiologic significance.[1] A megaloblastic type of anemia usually implies a deficiency of vitamin B_{12} or folic (pteroylglutamic) acid compounds; so some relation of infection and ascorbic acid deficiency to the metabolism of these compounds might be anticipated.

We have explored the relation of ascorbic acid deficiency to the development of folic acid deficiency, experimentally[2] and in megaloblastic anemia in infancy.[3] All the evidence indicates that the requirement for folic acid is increased by a deficiency of ascorbic acid, especially when so severe as to lead to scurvy.[4] This mechanism may be of importance in many infants with megaloblastic anemia, but in most infants megaloblastic anemia developed after a series of infections, even though the intake of ascorbic acid was unquestionably adequate.

It is to the latter group that the observations to be described in this report may apply. Considering the tendency for ascorbic acid to be depleted in the tissues during infections, one might suppose that infection, by producing a deficiency of ascorbic acid, could cause a disturbance of folic acid metabolism comparable to the

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From the Department of Pediatrics, College of Medical Sciences, University of Minnesota.

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1. Zuelzer, W. W., and Ogden, F. N.: Megaloblastic Anemia in Infancy, Am. J. Dis. Child. **71**:211, 1946.

2. May, C. D.; Sundberg, R. D.; Schaar, F.; Lowe, C. U., and Salmon, R. J.: Experimental Nutritional Megaloblastic Anemia: I. Nutritional Data and Manifestations of Animals, A. M. A. Am. J. Dis. Child. **82**:282, 1951.

3. May, C. D.; Nelson, E. N.; Lowe, C. U., and Salmon, R. J.: Pathogenesis of Megaloblastic Anemia in Infancy, Am. J. Dis. Child. **80**:191, 1950.

4. May, Sundberg, Schaar, Lowe, and Salmon.[2] May, Nelson, Lowe, and Salmon.[3]

situation in scurvy. While this may be true in some instances, we will show it is not a plausible explanation in all cases.[5]

SPONTANEOUS OCCURRENCE OF MEGALOBLASTOSIS WITH INFECTION IN MONKEYS

We had an opportunity in a colony of monkeys to follow the pattern of blood formation in the marrow during occasional isolated respiratory infections which appeared spontaneously among the animals. The monkeys under consideration were being fed cows' milk diets supplemented with an abundance of ascorbic acid (at least 50 mg. daily), orally and intramuscularly. In several monkeys in which acute infections developed the marrow was found to progress from a normal to a megaloblastic pattern. Other monkeys similarly infected revealed only a characteristic leucocyte response in the marrows with no trace of the megaloblastic type of reaction.

Analysis of the livers of these two groups of monkeys succumbing to infection revealed that those with megaloblastic marrows had much lower than normal levels of folic acid compounds in their livers. Those monkeys in which the marrow did not become megaloblastic had more nearly normal levels of folic acid compounds in the livers. A summary of the essential data from these monkeys [6] is provided in Table 1.

TABLE 1.—*Average Vitamin B_{12} and Folic Acid Compounds in Livers of Monkeys Dying of Respiratory Infection*
(Milk Diets, Abundant Ascorbic Acid)

	γ/Wet Gm.		
	B_{12} *	Folic Acid †	Folinic Acid ‡
Marrow normoblastic (died 7th to 12th day of experiments)	0.5	0.62	0.042
Marrow megaloblastic (died 44th to 166th day of experiments)	0.5	0.16	0.008
Average values in normal monkeys fed same diets for long periods *	1.00	1.10	0.026

* Vitamin B_{12} determined by microbioassay using Lactobacillus leichmannii.[6]
† Total folic acid as measured by microbioassay with Streptococcus faecalis after liberation of free folic acid from conjugates by hog kidney conjugase.[6]
‡ Free folinic acid (citrovorum factor) determined by microbioassay with Leuconostoc citrovorum.[6]

The question as to whether the infection depleted the tissues of ascorbic acid and thus provoked a deficiency of folic acid cannot be answered from this group of monkeys because the tissues were not analyzed for ascorbic acid. These were incidental observations rather than planned experiments.

It must be reemphasized at this point that infection was not the cause for depletion of folic acid and megaloblastosis in our previously reported experiments with scorbutic monkeys.[2] Careful clinical observation and microscopic examination of the tissues for evidence of infection excluded this explanation reasonably well.

5. Several forms of vitamin B_{12} and folic acid have already been described. For clinical purposes all forms will be grouped under the terms "vitamin B_{12}" and "folic acid compounds" unless specific designation of particular derivatives, such as folinic acid, will add clarity. The final biological actions of all the compounds grouped under vitamin B_{12} or folic acid are essentially those of the parent substances.

6. May, C. D.; Hamilton, A., and Stewart, C. T.: Experimental Megaloblastic Anemia and Scurvy in the Monkey: IV. Vitamin B_{12} and Folic Acid Compounds in the Liver, Diet, Urine and Feces and Effects of Therapy, Blood **7**:978, 1952.

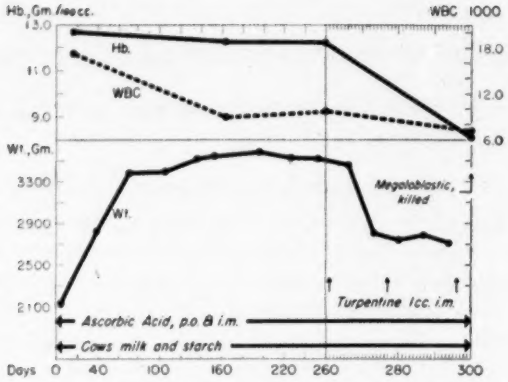

Fig. 1 (Monkey 73).—Megaloblastic anemia-turpentine abscess. Milk diet included abundance of ascorbic acid. For 260 days the animal thrived on this diet, and blood and marrow remained normal. Then the series of injections of turpentine was begun. After three injections within 39 days the marrow became megaloblastic. The animal was killed for tissue analyses (Table 4). Cells from the bone marrow are shown in Figure 2.

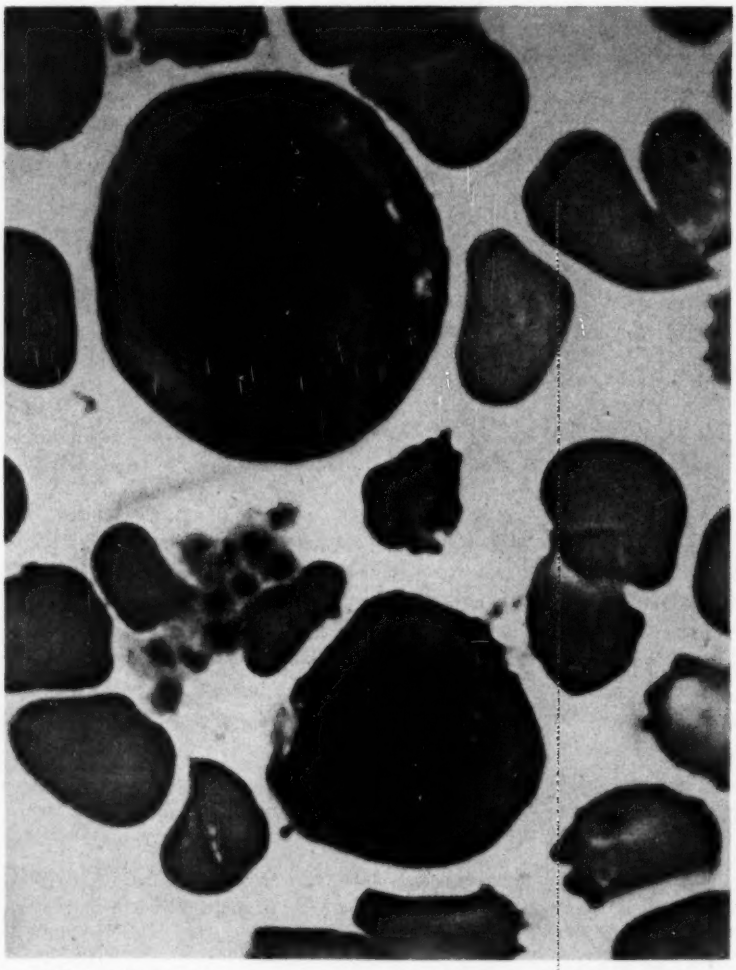

Fig. 2.—Megaloblasts from bone marrow of Monkey 73 (Fig. 1) on 39th day after turpentine injections were begun. Larger nucleated cell is a basophilic megaloblast and smaller one is an orthochromatic megaloblast.

Further evidence differentiating the scorbutic megaloblastic animals from those acquiring megaloblastosis following infection will be presented in the following experiments, contrived to study these relationships.

EXPERIMENTAL INDUCTION OF MEGALOBLASTOSIS BY TURPENTINE ABSCESS

It so happened that while we were interested in producing megaloblastic anemia in ascorbic-acid-deficient monkeys some other unrelated studies in our laboratory required the creation of sterile abscesses in monkeys. Because of our preoccupation with anemia we examined the bone marrow in the animals in which abscesses were being produced. The marrow samples were taken somewhat unsystematically at various intervals after the intramuscular injections of turpentine. The course of such an animal (Monkey 73) which received turpentine injections intramuscularly is depicted in Figure 1. This animal had been fed a diet of cows' milk to which starch had been added. Optimal tissue saturation with ascorbic acid was assured by providing 50 mg. orally each day and 100 mg. intramuscularly once a week. This monkey had been maintained in good health on this regimen for 260 days; no anemia or leucopenia developed, and the marrow remained normal. One cubic centimeter of turpentine was injected into the muscles of the legs on the 261st, 277th, and 296th days. The appetite, activity, and weight declined during the series of turpentine injections, but diarrhea did not develop. Marrow samples examined from time to time revealed only the leucocyte activity expected with suppurative processes until 4 days after the third injection of turpentine (39 days after the first injection), when a definite megaloblastic pattern of hemopoiesis was encountered (Fig. 2). The leucocyte series also had the changes characteristically found in megaloblastosis.

On the basis of this chance discovery of megaloblastosis following turpentine injections we set about to repeat the observation, to determine the tissue concentrations of ascorbic acid, vitamin B_{12}, and folic acid compounds, and to follow the effect of therapy on the marrow. Another animal, which had been thriving on a diet of cows' milk and starch for 150 days (Monkey 72), and four animals (Monkeys 105, 118, 135, 138) recently received from an animal dealer and placed on a diet of cows' milk [7] were selected for study. The hemoglobin and bone marrow

7. Experimental Diet 4F

Dried Cows' Milk, 12 gm.
Water to make 100 cc.
5% $CuSO_4$, 1 drop per 100 cc.

Daily Supplement, orally
Ascorbic Acid, 50 mg.
Vitamin A, 4000 I. U.
Vitamin D, 400 I. U.
15 mg. *d*-alpha tocopherol acetate
} water-miscible
Elixir ferrous gluconate, 4 cc.

Weekly Supplement, orally
Vitamin B_{12}, 15 γ.
Thiamine hydrochloride, 5 mg.
Riboflavin, 2 mg.
Nicotinamide, 75 mg.
Sodium pantothenate, 2.5 mg.
Pyridoxine hydrochloride, 5 mg.

Monkeys 72 and 73 were given 100 mg. of ascorbic acid intramuscularly weekly as well as 50 mg. orally throughout the experiments.

Details concerning the usual manifestations of monkeys fed this type of diet have already been published.[2]

were found to be normal in each animal, and then 1 cc. of turpentine was injected intramuscularly. The turpentine gave rise within a day to marked cellulitis, the animals became mildly ill and ate less for a few days, but they quickly resumed normal behavior except for favoring the affected leg. Fluctuation soon developed in the injected area, and usually in about a week a purulent material burrowed to the surface and drained freely before the wound healed. The purulent material was cultured and found to be sterile. During this sequence of events, after the first injection of turpentine, the marrow revealed activity in the leucocyte series with only minor changes in the erythrocyte series. After two or more injections a characteristic megaloblastic metamorphosis was observed in the erythrocyte series. The time and number of injections required to produce a megaloblastosis was variable. The composite data from the experimental animals may be seen in Table 2. The megaloblastosis finally achieved in all six monkeys given turpentine

TABLE 2.—*Summary of Data on Monkeys in Which Megaloblastosis Was Induced by Turpentine Abscesses*
(Milk Diets, Abundant Ascorbic Acid)

Monkey	Turpentine Injected, (Day of Experiment)	Megaloblastic (Day of Experiment)	Hemoglobin,* Gm./100 Cc.	Leucocytes* per Cu. Mm.	Treatment †	Effect on Marrow
72	1, 37, 105	73	10.8	5,870	15 γ B_{12} intramuscularly, 2 days	No effect; died
73	1, 16, 35	39	8.1	7,150	None	Killed 39th day for tissue analyses
105	1, 17, 25	32	9.0	6,900	Folic acid heptaglutamate ‡ orally, 12 days	No effect; killed on 44th day for tissue analyses
118	1, 17, 25, 36	40	9.2	4,800	None	Killed on 41st day for tissue analyses
135	1, 17, 33, 50, 59, 90	65	....	.....	30 γ B_{12} intramuscularly, 3 days	No effect in 7 days
					15 mg. folic acid intramuscularly, 2 days	Normoblastic 11 days later
138	1, 17, 33, 50, 59	65	....	.....	Abscess allowed to heal	Normoblastic by 74th day

* Average normal values [8]: hemoglobin 12.7 gm. per 100 cc.; leucocytes 15,400.

† Ascorbic acid continued and abscesses maintained through trials of therapy, except in 138 abscess was allowed to heal.

‡ A concentrate of folic acid heptaglutamate derived from yeast was assayed in our laboratory to contain 0.79% heptaglutamate. The daily oral dose of 37 mg. provided the equivalent of 100 γ folic acid activity as determined by treatment with conjugase and assay with Str. faecalis. The concentrate was supplied by Dr. Richard D. Greene, of E. R. Squibb & Sons.

injections was typical in every respect, including characteristic alterations in the leucocytes, and was quite like the marrow seen in megaloblastosis in infants and in scorbutic monkeys. Our criteria for designating a marrow as megaloblastic have been fully discussed and illustrated in other publications from this laboratory.[2, 8] An illustration typical of the megaloblasts which appeared in the marrows after a series of turpentine injections is provided in Figure 2. When megaloblastosis was established the animals failed rapidly, became very anorexic and apathetic, and lost weight precipitously, and the fur appeared lusterless and disheveled. Two animals acquired mild diarrhea, but the stools remained normal in the others. It is interesting to note that although large areas of necrosis were present at the sites of the turpentine injections a leucopenia rather than leucocytosis was found in the peripheral

8. Sundberg, R. D.; Schaar, F., and May, C. D.: Experimental Nutritional Megaloblastic Anemia: II. Hematology, Blood **7**:1143, 1952.

blood. This is characteristic in folic acid deficiency. At the time of megaloblastosis the hemoglobin was 8 to 10 gm., compared with the average value of 12.7 gm. found in control monkeys. The animals were killed for tissue studies or treated as soon as megaloblastosis was discovered.

The time required to produce scurvy in monkeys by milk diets devoid of ascorbic acid is fairly uniform, averaging 78 days. Megaloblastosis rarely develops until overt signs of scurvy appear, usually after about two weeks of conspicuous evidence of scurvy. Megaloblastosis associated with spontaneous infections naturally occurred at most variable times. Megaloblastosis induced by turpentine injections follows a somewhat more regular pattern than that associated with spontaneous infections and develops more quickly than when induced by scurvy. These points are demonstrated by typical data in Table 3. One significance of this information is to indicate

TABLE 3.—*Megaloblastic Anemia in Monkeys*

	Day of Occurrence in Experiments Under Different Circumstances			
	Ascorbic Acid Deficient		Ascorbic Acid Adequate	
	Scurvy	Megaloblastic	Infection	Turpentine Abscesses
	70	90	43	32
	70	90	44	39
	72	92	99	40
	83	98	111	65
	84	102	160	65
	88	119	..	73
Average	78	90	92	52

TABLE 4.—*Vitamins in Livers of Monkeys on Milk Diet*
(γ/gm., wet, average values)

	Total Animals	Ascorbic Acid	B_{12}	Total Folic Acid	Free Folinic Acid
Controls,[6] adequate ascorbic acid	5	129	1.0	1.10	0.026
Turpentine abscess, adequate ascorbic acid					
Megaloblastic	3	151	0.8	0.20	0.014
Scorbutic					
Megaloblastic	7	8	0.6	0.14	0.006
Normoblastic, supplementary folic acid	1	4	0.6	1.43	.....
Infection, adequate ascorbic acid					
Megaloblastic	5	103	0.5	0.16	0.008
Normoblastic	6	...	0.5	0.62	0.042

that it is quite unlikely that spontaneous infection, which would be acquired irregularly, could be a primary factor in the regularity of appearance of megaloblastosis in the course of scurvy.

Data concerning the liver content of vitamin B_{12}, the folic acid compounds, and ascorbic acid found in monkeys in which megaloblastosis developed in the different circumstances mentioned above are presented in Table 4. Several features should be noted which distinguish these groups. The turpentine-injected group had considerably lower than normal folic acid level in the liver even though the

ascorbic level was maintained at the level of the controls by supplementation of the diet. In the group suffering spontaneous infections those in which megaloblastic marrows developed had much lower levels of folic acid in the liver than similarly infected animals in which the marrow remained normoblastic. An animal rendered scorbutic but given supplementary folic acid did not acquire megaloblastosis, and the liver content of folic acid was maintained at a normal level in the presence of severe scurvy. The concentration of vitamin B_{12} was less affected in all the groups.

EFFECTS OF TREATMENTS

The turpentine abscesses were maintained active during trials of therapy, by repeated injections if necessary. The responses in the marrows to various treatments (Table 2) correspond to the findings in the liver analyses (Table 4). Neither vitamin B_{12} nor ascorbic acid was able to prevent or to eliminate the megaloblastosis in the marrow resulting from turpentine injections. The same had been found to be true of the megaloblastosis arising in monkeys in the course of spontaneously acquired infection. Folic acid was promptly effective in eliminating the megaloblastic pattern from the marrow of both the turpentine-injected and the spontaneously infected monkeys. Either ascorbic acid or folic acid will eliminate the megaloblastosis complicating scurvy, but vitamin B_{12} alone is without effect. When the turpentine abscess was allowed to heal, the megaloblastic reaction in the marrow disappeared simultaneously and was replaced by a normal normoblastic pattern without any therapy. The animal improved correspondingly. Oral administration of a heptaglutamate of folic acid, in a larger amount than would be obtained from the diet or intestinal flora, was unable to furnish an animal with sufficient folic acid to cure megaloblastosis while the turpentine abscess persisted, even though the ascorbic acid intake was abundant. We have found folic heptaglutamate to be poorly absorbed by monkeys; only 4% of an oral dose appears to be absorbed.

Important factors in the development of megaloblastic anemia so readily following infection or turpentine abscess in monkeys are (1) the low content of folic acid compounds in the diet, (2) poor absorption of the conjugated form of folic acid that occurs in food and the intestinal contents, and (3) the immaturity of the animals and increased requirements for growth.

COMMENT

Infants are probably unable to synthesize folic acid or vitamin B_{12} but depend upon such sources as food and the production of these vitamins by the intestinal bacterial flora to meet their requirements. The steps followed in the absorption and utilization of vitamin B_{12} and folic acid compounds are not yet known in detail but may be roughly outlined as in Table 5. It is apparent in this scheme that numerous opportunities are afforded for pathological disturbances to interfere with absorption and utilization of these vitamins. It may be noted in Table 6 that, except for the dietary intake of vitamin B_{12} and folic acid, all the other factors which may lead to a deficiency of these substances pertain to abnormal or diseased persons. The milk feedings commonly employed in early infancy all contain about the same, but rather small, amounts of vitamin B_{12} and folic acid compounds (Table 7). Normal infants receiving such diets, when the diets are complete and balanced in other vitamins, thrive on the amounts of vitamin B_{12} and folic acid ingested or produced by the

intestinal bacteria. It is in the sick and abnormal infants, in whom ingestion, intestinal synthesis, absorption, or utilization may be disturbed or for whom requirements may be increased, that one might expect to find evidences of deficiency of folic acid or vitamin B_{12}.

TABLE 5.—*Steps in Absorption and Utilization of Vitamin B_{12} and Folic Acid Compounds*

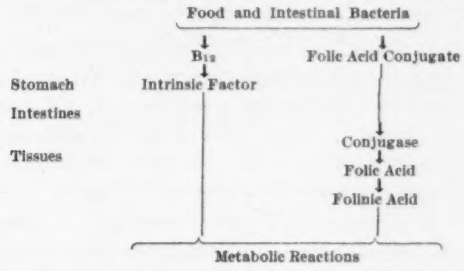

TABLE 6.—*Possible Factors Leading to Deficiency or Increased Requirements of Vitamin B_{12} or Folic Acid*

Deficiency of vitamin B_{12} or folic acid in infancy could result from the following:

- Deficient diet
- Inadequate synthesis by intestinal bacteria
- Lack of intrinsic factor in stomach
- Defective intermediary metabolism
- Inadequate stores from mother

Increased requirements could result from the following:

- Infection
  - Loss of sparing effects
  - Rapid growth
  - Prematurity
  - Dietary imbalance
  - Vitamin inhibitors or antagonists

TABLE 7.—*Average Content of Common Milk Feedings**

	Vitamin B_{12}, γ/L.	Folic Acid, γ/L.
Human milk	2	3
Fresh cows' milk formula †	2	3
Dried cows' milk formula †	2	3
S-M-A® ‡	2	3
"Similac" ‡	2	3
Evaporated cows' milk formula †	2	3
Evaporated goats' milk formula †	2	2

* Data were obtained in our laboratory by microbioassay procedures yielding total vitamin B_{12} and folic acid compound activities.[6]
† Customary ⅔ milk, ⅓ water dilutions.
‡ Normal dilutions.

The most definitive sign of deficiency of folic acid or vitamin B_{12} is the appearance of a megaloblastic type of hemopoiesis in the bone marrow. Failure in growth,

fatty changes in the liver, and other phenomena also may be attributed to deficiency of these vitamins but are much less specific, or even equivocal, signs. Apparently both vitamin B_{12} and folic acid are required for normal hemopoiesis. In order to determine which is the predominant deficiency in a patient with megaloblastic anemia, vitamin B_{12} must be tested first because all clinical types of megaloblastic anemia will respond to large doses of folic acid regardless of the pathogenesis.

APPLICATION TO MEGALOBLASTIC ANEMIA OF INFANCY

The majority of infants recognized to have acquired megaloblastic anemia may be included in three broad groups: those responding to vitamin B_{12}; those failing to respond to vitamin B_{12} but effectively treated with folic acid, and those acquiring a deficiency of folic acid in association with a lack of ascorbic acid, in which case the megaloblastosis may be eliminated by either folic acid or ascorbic acid. Charts of infants illustrating each of these groups are presented in Figures 3, 4, and 5.

The infant whose chart is presented in Figure 3 illustrates the development of megaloblastosis as a complication of scurvy and its disappearance on treatment with

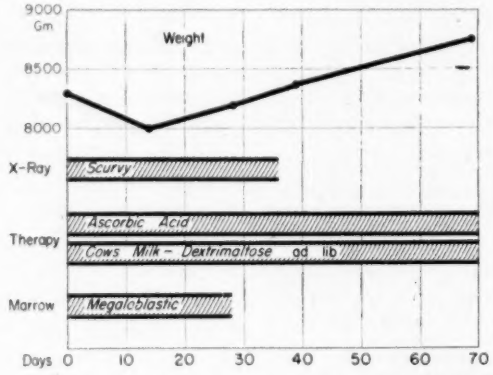

Fig. 3.—Scurvy with megaloblastic marrow. An 8-month-old infant admitted because of signs of scurvy and found to have megaloblastic anemia. Treated without changing diet by large doses of ascorbic acid alone. Marrow gradually reverted to normoblastic pattern during period of 28 days. Uneventful lasting recovery.

ascorbic acid alone. Ordinarily it would be preferable to treat such an infant with both folic acid and ascorbic acid.

The infant whose chart is presented in Figure 4 illustrates the situation in which a deficiency of folic acid predominates; as can be seen, ascorbic acid did not prevent the megaloblastosis and vitamin B_{12} could not cure it. Folic acid was promptly effective. The infant carried the burden of a chronic infection, pyuria, from birth. Other factors, such as antibiotic therapy, may have contributed to the deficiency of folic acid. To be noted is the marked leucopenia characteristic of folic acid deficiency.

In the infant whose chart is presented in Figure 5 the megaloblastosis was eliminated by vitamin B_{12} alone, indicating that this was the predominant deficiency; ascorbic acid intake was known to be adequate. Infection was not a conspicuous feature in the clinical history or findings. This patient serves to indicate that infants

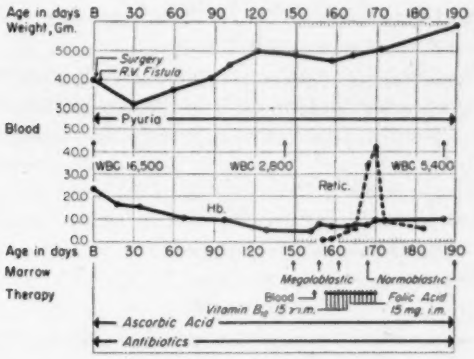

Fig. 4.—Megaloblastic anemia—response to folic acid following failure of ascorbic acid and vitamin B_{12}. A newborn infant with imperforate anus. Surgery second day. Complicating recto-vesicle fistula and pyelonephritis. Colostomy required on fourth day. Hemoglobin fell steadily in spite of four transfusions of blood prior to 150th day, when a megaloblastic pattern was found in the marrow. The blood urea nitrogen stabilized at 15 mg. per 100 cc. Various antibiotics were employed, orally and parenterally, throughout course. Ascorbic acid provided in 50 to 100 mg. doses orally from birth. Roentgenograms revealed no evidence of ascorbic acid deficiency. Vitamin B_{12} administered intramuscularly had no effect on blood or marrow in 10 days. Marrow promptly became normoblastic after folic acid therapy and there was marked reticulocytosis. Subsequent course was one of striking improvement in clinical symptoms and marrow remained normal with continued oral folic acid therapy. Therapy with iron before and after above therapy was without additional effect.

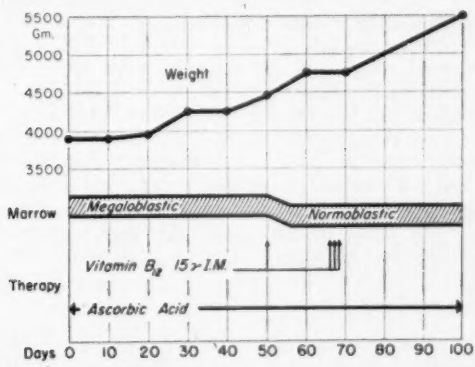

Fig. 5.—Megaloblastic anemia—response to vitamin B_{12}. Infant weighed 2,700 gm. at birth. He had a cleft palate and was kept in a hospital 22 days after birth because of difficulty in feeding. Reared on standard cow's milk formula, but always difficult to feed. Received adequate supplements of ascorbic acid and vitamins A and D. No diarrhea or infections had been noted. When first seen at 10 weeks of age was found to be undernourished and to have a hemoglobin value of 8 gm. per 100 cc. and a megaloblastic pattern in the marrow. Intensive therapy with ascorbic acid alone had no effect. Vitamin B_{12} caused prompt return of the marrow to normal and marked clinical improvement which persisted for many months without further vitamin B_{12} therapy.

may acquire a deficiency of vitamin B_{12}, but further clarification of the pathogenesis is required. The prematurity, cleft palate, and consequent nutritional difficulties in this infant may have been important. The role of intrinsic factor in the absorption of vitamin B_{12} in infancy needs to be studied.

The practical consequences are these: Normal infants on the usual feeding regimens including adequate ascorbic acid do not require supplementary vitamin B_{12} or folic acid compounds. Sick infants require special consideration, since infection, ascorbic acid deficiency, and many other pathological circumstances may lead to increased requirements for vitamin B_{12} and folic acid. In cases of severe or prolonged infections it would probably be wise to include additional amounts of vitamin B_{12} and folic acid in the treatment during the infection and immediate convalescent period.

SUMMARY

The spontaneous occurrence of megaloblastic anemia in association with infection in infants and in monkeys is described.

Megaloblastic anemia was induced experimentally in monkeys by producing abscesses with intramuscular injections of turpentine.

Analyses of the liver for ascorbic acid, vitamin B_{12}, and folic acid compounds in natural and experimental infections are presented.

The low content of folic acid compounds in the liver in both natural and experimental infections and the elimination of megaloblastosis from the marrow by folic acid, but not by vitamin B_{12} or ascorbic acid, leads to the conclusion that infection can cause a deficiency of folic acid compounds.

The application of these observations to the various types of megaloblastic anemia seen in infants and to treatment is discussed.

Case Reports

ALCALIGENES FAECALIS MENINGITIS COMPLICATED BY HYDROCEPHALUS IN A PREMATURE TWIN

Report of Case; Intramuscular Chloramphenicol Therapy

ROBERT ORR WARTHEN, M.D.
KENSINGTON, MD.

A REVIEW of the literature disclosed 56 cases of meningitis occurring in premature infants.[1] Only 21 of these were confirmed by bacteriologic culture,[2] in 11 the meningitis being due to Escherichia coli and in the remaining, in declining order of frequency, to Streptococcus, Diplococcus pneumoniae, "Gram-negative bacilli," Klebsiella pneumoniae, Aerobacter aerogenes, and Esch. coli var. acidi lactici. Two of the 56 infants recovered.[3] One weighed 930 gm. when Esch. coli meningitis was diagnosed at 20 days of age. Streptomycin effected a complete recovery. The other weighed 2,400 gm. at 18 days of age, when the diagnosis of meningitis due to a proteolytic Gram-negative bacillus was established. Complete recovery followed sulfathiazole therapy.

Eight cases of meningitis due to organisms of the genus Alcaligenes have appeared in the literature,[4] one attributed to Alcaligenes bookeri [4e] and the remaining to Alcaligenes faecalis.[5] Two newborn infants died, one receiving no specific

From Children's Hospital, Washington, D. C.

1. (*a*) Kagan, B. M.; Hess, J. H.; Mirman, B., and Lundeen, L.: Meningitis in Premature Infants, Pediatrics **4**:479, 1949. (*b*) Koplik, H.: Meningitis in Newborn and in Infants Under Three Months of Age, Arch. Pediat. **33**:481, 1916. (*c*) Glaser, J.: Cerebrospinal Fluid of Premature Infants, Am. J. Dis. Child. **40**:741, 1930. (*d*) Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children with Special Reference to Age-Incidence and Bacteriologic Diagnosis, J. Pediat. **2**:696, 1933. (*e*) Craig, W. S.: Meningitis in Newborn, Arch. Dis. Child. **11**:171, 1936. (*f*) Schulman, B. H., and Johnson, M. S.: Case of Meningitis in Premature Infant Due to Proteolytic Gram-Negative Bacillus, J. Lab. & Clin. Med. **29**:500, 1944. (*g*) Cruickshank, J. N.: Child Life Investigations: Causes of Neo-Natal Death, Medical Research Council, Special Report Series, No. 145, London, His Majesty's Stationery Office, 1930. (*h*) Hess, J.; Mohr, G., and Bartelme, P.: Physical and Mental Growth of Prematurely Born Children, Chicago, The University of Chicago Press, 1934.

2. Footnote 1 *a*, *b*, *c*, *d*, *e*, and *f*.

3. Footnote 1 *a* and *f*.

4. (*a*) Bischoff, H. W.; Recinos, A., Jr.; Anderson, W. S., and Rice, E. C.: Alkaligenes Fecalis Bacteremia and Meningitis: Report of Two Cases in Newborn Infants, J. Pediat. **32**:558, 1948. (*b*) Gatewood: Bacillus Fecalis Alkaligenes Meningitis, Am. J. Surg. **12**:435, 1931. (*c*) Mason, R. J.: Acute Meningitis Due to Bacillus Fecalis Alcaligenes, J. Pediat. **4**:514, 1934. (*d*) Spray, B. S., and Hawk, F. L.: Cerebrospinal Meningitis: Case Report with Unusual Bacteriological Findings, West Virginia M. J. **30**:564, 1934. (*e*) Kutscher, G. W., Jr.: Alkaligines Bookeri Meningitis: Review of Literature on Gram-Negative Bacillus Meningitis, Arch. Pediat. **54**:610, 1937. (*f*) Voorhies, N. W., and Wilen, C. J.: Alcaligenes Faecalis Bacteremia, Am. J. M. Sc. **204**:719, 1942. (*g*) Terry, L. L.; McBane, J. K., and Dean, K. F.: Bacteremia and Acute Meningitis Due to Alcaligenes Faecalis, J. Lab. & Clin. Med. **32**:1262, 1947.

5. Footnote 4 *a*, *d*, *f*, and *g*.

therapy and the other penicillin and sulfadiazine. The ages of the remaining six patients ranged from 4½ months to 42 years. One died without specific treatment, and five recovered, three with no specific therapy, one with sulfadiazine, and one with streptomycin and sulfadiazine.

Herein is reported a case of A. faecalis meningitis in a premature infant. Intramuscular administration of chloramphenicol effected a rapid recovery; however, complicating hydrocephalus resulted in death six months later. This is the third premature infant to recover from meningitis. It is the first recorded case of A. faecalis meningitis in a premature infant and the ninth of the genus Alcaligenes to appear in the literature. In view of recent advances in antibiotic therapy and chemotherapy, the early recognition of similar cases becomes of increasing importance.

REPORT OF A CASE

D. L., the firstborn of female premature twins, weighed 1,930 gm. at birth. Satisfactory progress was maintained until the 9th day of life, when her temperature rose to 100.2 F., she became quite listless, and she refused to swallow her formula. Her weight was 1,761 gm. Examination at that time showed no significant abnormalities, with the exception of a flat somewhat tense anterior fontanelle. Examination of the spinal fluid showed the following: xanthochromic fluid; globulin, 4+; total protein, 690 mg. per 100 cc.; erythrocytes, 800 per cubic mm.; leucocytes, 450 per cubic mm.; differential count, 70% neutrophiles and 30% lymphocytes; smear, many Gram-negative bacilli; culture, A. faecalis. Intramuscular administration of chloramphenicol in a dosage of 250 mg. twice a day (approximately 250 mg. per kilogram of body weight for 24 hours) was begun upon receipt of the smear report. At that time her temperature had risen to 102 F., and four hours later frequent intermittent clonic convulsions appeared. These were controlled with intramuscular administration of phenobarbital. Eight hours after initiation of antibiotic therapy her temperature had returned to normal. A blood count at that time revealed 11 gm. of hemoglobin per 100 cc., 3,800,000 erythrocytes, and 24,800 leucocytes, with 39% lymphocytes, 20% segmented forms, 39% band forms, and 2% young forms. Sensitivity tests disclosed the organism to be most susceptible to chloramphenicol and moderately sensitive to aureomycin hydrochloride. Streptomycin and oxytetracycline ("terramycin") were totally ineffective.

During the following two weeks occasional episodes of Cheyne-Stokes respirations, pallor, and clonic seizures were controlled with oxygen and phenobarbital sodium.

A spinal tap performed after one week of treatment yielded only a small amount of yellow fluid, approximately 70% of which had coagulated within 20 minutes of its withdrawal. Because of insufficient fluid only a smear and a culture could be studied, neither of which disclosed any significant abnormalities. Bilateral subarachnoid taps disclosed only a small amount of slightly xanthochromic fluid. The head circumference was 30.8 cm., and the anterior fontanelle was flat; however, in view of the suspicion of a high concentration of lumbar spinal fluid protein as evidenced by coagulation of the fluid, a cerebrospinal block was postulated.

Eight days later the anterior and posterior fontanelles were full and tense, and the sagittal suture was widening. The head circumference was 33 cm. A spinal fluid examination disclosed yellow fluid, 1,760 mg. protein per 100 cc., 80 mg. sugar per 100 cc., and 89 cells per cubic millimeter, with 100% lymphocytes. No organisms were detected in the smear, and the culture was sterile. As a gesture in relieving the suspected cerebrospinal block, 4 cc. of air was injected into the lumbar spinal subarachnoid space. Bilateral subarachnoid taps revealed no excessive extradural, subdural, or subarachnoid fluid.

The chloramphenicol treatment was discontinued after 17 days, and at discharge, 33 days after the onset of meningitis, she weighed 2,160 gm., and her head circumference measured 36.25 cm. At 6 months of age, when her head circumference had reached 59 cm., she suddenly expired.

Autopsy Findings.—With the exception of confluent bronchopneumonia, the pertinent findings were limited to the brain.

The head circumference measured 59 cm. All cranial sutures were widely separated, the anterior fontanelle measuring 17 cm. in its transverse diameter. In some areas the skull was parchment thin. The brain weighed 3,005 gm., as contrasted to the normal weight of 66 gm., and all convolutions were indistinct and flattened. The cerebral cortex was reduced to an average thickness of 1 cm., with several areas of transparency. The ventricular system contained approximately 1,500 cc. of yellow fluid, was uniformly dilated, and contained no internal obstruction. The meninges over the entire surface of the pons and the medulla were markedly thickened by dense fibrous adhesions, with apparent resultant obliteration of the subarachnoid space. The plastic adhesions prevented identification of the foramina of Luschka and Magendie. The subcortical nuclei, including the basal nuclei, showed extensive atrophy.

Microscopic examination disclosed marked cellular degeneration and subpial fibrosis of the cerebrum, more prominent in the ventricular walls. The subarachnoid space of the pons and medulla contained a fibrous and fibrinous exudate with chronic inflammatory cells and pigment-laden wandering cells. The ependymal linings of the choroid plexuses were normal, as were the arachnoid villi.

The pathological diagnosis was made as follows: (1) internal hydrocephalus secondary to chronic adhesive basilar arachnoiditis; (2) parenchymal degeneration and fibrosis of the cerebrum, and (3) confluent bronchopneumonia.

SUMMARY

A case of Alcaligenes faecalis meningitis in a 9-day-old premature twin is reported. Although intramuscular administration of chloramphenicol effected a rapid recovery from the meningitis, complicating hydrocephalus resulted in death six months later.

Only two other premature infants have been known to recover from meningitis; however, recent advances in antibiotic therapy and chemotherapy make the early recognition of such cases of ever increasing importance.

Meningitis caused by bacteria of the genus Alcaligenes has been recorded only eight times previously. This is the first to occur in a premature infant.

The literature is reviewed.

3716 Howard Ave.

Obituaries

OSCAR MENDERSON SCHLOSS, M.D.
1882-1952

Dr. Oscar Menderson Schloss did not awaken from his sleep on the morning of Oct. 13, 1952. This peaceful death brought to an end 70 years of an active life and 47 years of a notable career in medicine.

Oscar Schloss was born in Cincinnati, June 20, 1882, and he graduated from The Johns Hopkins University School of Medicine in 1905. After three years of in-resident training, he embarked on a threefold professional career of research worker, medical educator, and practicing pediatrician. It would be difficult to say in which of these fields he contributed most, for he was preeminent in all.

Except for a span of two years (1922 and 1923), during which time Dr. Schloss occupied the chair of pediatrics at Harvard Medical School, his academic activities were centered in the Cornell University Medical College (1919 to 1952), the New York Nursery and Childs Hospital (up to 1932), and the New York Hospital (1932 to 1952). He served these institutions with distinction as professor and professor emeritus of pediatrics and as pediatrician-in-chief, attending pediatrician, and consulting pediatrician. During the 33 years of his academic life, Dr. Schloss gave unsparingly of himself to students and staff alike. His skill as a teacher, his clinical acumen, and his integrity as an investigator aroused in them an admiration, respect, and affection which were memorable. His colleagues sought him out for his wisdom and experience, and they were always rewarded by his good and generous guidance. This high regard and esteem were shared by his medical peers. Dr. Schloss was a member of the American Pediatric Society (president, 1932-1933), the Society for Pediatric Research, the American Society for Clinical Investigation, the Society for Experimental Biology and Medicine, and other scientific societies. In 1925 he gave a Harvey Lecture on "The Intestinal Absorption of Antigenic Protein," and he was elected to honorary membership in that Society. He served as an editor of the AMERICAN JOURNAL OF DISEASES OF CHILDREN from 1924 to 1950. These honors were accorded to him in recognition of his many fundamental contributions to medicine in the fields of infantile diarrhea and dehydration, eczema, ketosis, and others. His pioneer work on food allergy presented in 1912 initiated the beginning of a new era in this field in the United States. When Oscar Schloss learned that his teacher, John Howland, was submitting a paper for publication on the mechanism of acidosis in infantile diarrhea, a problem which he had independently investigated and about which he had reached similar conclusions, he characteristically ceded any claim to priority and deferred his report. In the words of Edwards A. Park, "It was an act of courtesy and generosity from a younger to an older man which deserves unstinted praise."

In his research work, Dr. Schloss revealed the same humility and modesty, integrity and honesty, self-criticism, and keen judgment as in his contacts with

students and staff. His mastery of the written word is reflected in his publications, as was his mastery of the spoken word in his lectures and ward rounds. The conclusions reported in his scientific papers remain as valid today as when they first appeared.

In medical practice, Dr. Schloss was equally revered by his patients. His love of children, his sympathetic understanding of parents, his rapport with referring

OSCAR MENDERSON SCHLOSS
1882-1952

physicians, together with his great store of basic knowledge and broad experience, were some of the attributes which made him a great practitioner and a superb consultant.

Oscar Schloss is survived by his devoted wife, Rowena Farmer, and one son, Oscar Menderson, Jr. His students, friends, colleagues, and patients share with them a great sorrow in his inestimable loss. His gentle yet forceful spirit led with a kindly and just light all who sought his wise counsel and advice.

Society Transactions

SOCIETY FOR PEDIATRIC RESEARCH

Horace L. Hodes, M.D., *President*

Sydney S. Gellis, M.D., *Secretary-Treasurer*

Twenty-Second Annual Meeting, Old Point Comfort, Va., May 5, 6, and 7, 1952

Second Session

Monday, May 6

(Concluded from Page 648)

Studies on the Agent of Infectious Hepatitis: III. The Effect of Skin Tests for Infectious Hepatitis on the Incidence of the Disease During an Outbreak in a Closed Institution. Dr. Miles E. Drake, Baltimore; Dr. Charles Ward, Owings Mill, Md.; Dr. Joseph Stokes Jr., Washington, D. C.; Dr. Werner Henle, Philadelphia; Dr. George C. Medairy, Owings Mill, Md.; Dr. François E. Mangold, Perrysville, Pa., and Dr. Gertrude Henle, Philadelphia.

(This article will appear in full in a forthcoming issue of the *Journal of Experimental Medicine.)*

In an effort to determine the meaning of positive and negative skin tests for infectious hepatitis in terms of immunity or susceptibility, about one-quarter of the inmates with negative histories of jaundice in a closed mental institution were given intradermal injections of antigen (and corresponding control material) at the onset of an outbreak of the disease. Of these, 144 had a positive reaction and 176 a negative reaction. Although the epidemic continued for one year, few cases of jaundice occurred in the skin-tested group. Among the 825 persons not skin tested, 112 cases of jaundice were recorded, or an incidence of 13.6%, whereas only 5 cases were noted among 320 previously skin-tested persons, or an incidence of 1.6%. In one of the latter cases there had been a positive reaction. In two of the cottages, housing boys and girls of the youngest age group (4 to 14 years), respectively, the incidence of jaundice was highest. Yet the same relative difference in the incidence of jaundice between skin-tested (mostly negative) and non-skin-tested persons was apparent. Examination of the records of these children as to length of stay at the institution failed to reveal an inadvertent selection thus excluding the possibility that the skin-tested group contained larger numbers of children immunized by exposure to infectious hepatitis during an outbreak which had occurred 5 to 6 years previously. These data suggest that the skin test antigen had altered the susceptibility. Possible explanations for this observation have been discussed.

DISCUSSION

Dr. David Y. Hsia, Boston: I should like to ask Dr. Drake three questions about the use of the skin test in infants under 6 months of age: 1. Has he done any skin testing on infants with hepatitis proved by liver biopsy? As we know, diagnosis is unusually difficult in this age group because flocculation tests do not always become positive in hepatitis as in older children and adults. The skin test would, therefore, be invaluable in diagnosis. 2. Has he tried skin testing the infants born of mothers who had infectious hepatitis during pregnancy? One wonders whether the test might be positive as a result of transmission of the virus from mother to child, as demonstrated by Wolman and Stokes, without the infant's clinically showing hepatitis. 3. Has he attempted to use the skin-testing material on infants to see whether it is effective in preventing hepatitis?

Dr. Albert B. Sabin, Cincinnati: I will be frank that the purpose of my remarks is to inject a certain amount of doubt into the interpretation of these data, and I will exaggerate for emphasis.

We are presented here with a striking, statistically significant difference in the incidence of hepatitis among those who were skin-tested and those who were not. The material used for

skin testing is supposed to contain virus in inactive form, and the deduction that one might draw from the observation is that either the inactivated virus or a small amount of residual active virus in the particular preparations used immunized a large proportion of the persons tested.

Now, how complete is the evidence that the chick embryo material contained hepatitis virus before it was inactivated for skin-test purposes? First of all, it has been demonstrated that such material has produced "hepatitis without icterus" in human volunteers and that on subsequent challenge with "human hepatitis virus" most of these volunteers were resistant. Since not all people, presumably because of naturally acquired immunity, react to an inoculation of active "human hepatitis virus," we have no way of knowing whether most of the volunteers used were not spontaneously immune. The demonstration that blood drawn from one of the volunteers having "hepatitis without icterus" after inoculation with chick embryo material produced hepatitis with icterus in other volunteers is marred by the fact that the donor of this "icterogenic" blood himself acquired hepatitis when he was challenged with "natural human virus." (This case was recently reported by Drake and his associates to the American Association of Immunologists.) It is, after all, possible that this donor was a spontaneous carrier of so-called serum hepatitis virus or of another virus serologically unrelated to the one used to inoculate the chick embryos. There may be other explanations, but the point is that the data on this score are not as unequivocal as one would like to have them.

Next, the chick embryo material used for the skin tests is believed to contain an antigen specific for the hepatitis virus, because positive skin tests have on a number of occasions been obtained for 95% of recent convalescents from hepatitis with jaundice, while only about 45% of controls without a history of jaundice had similar positive skin reactions. This observation may indeed mean that the controls, showing positive skin tests, are immune because of naturally acquired inapparent infections—but it may also mean something else. The reported neutralization of the skin-test antigen by serum obtained after, but not before, experimental infection of human beings with infectious-hepatitis virus indeed points to specificity if it can be shown that it is a reproducible phenomenon and that sera taken during the acute and convalescent phases from patients with other infections will not have the same effect.

I am not unaware of the difficulties involved in this kind of work and of the altogether admirable perseverance of Dr. Stokes, Dr. Drake, and their associates, but I should like to know before accepting their results that a virus of hepatitis is indeed involved.

I should like to see an experiment in which a sufficiently large number of persons who have positive reactions with the skin-test material fail to have hepatitis after inoculation of the virus immediately after the skin test is read, while a significant number of controls with negative skin reactions, similarly inoculated with virus, acquire the disease. Some such work may have already been done, and comments of the authors would be appreciated.

Now with regard to the study just reported, one would like to know not only how many of the skin-tested institutional inmates who proved to be so highly resistant during the course of the natural epidemic showed positive skin reactions but also what proportion of those who had negative reactions to begin with had positive reactions when retested at the end of the epidemic. It seemed to me that only about 20 persons were retested and that about 60% had positive reactions. I may be wrong in this, but 60% of so small a number of persons who have just come through an epidemic is not strikingly different from the 45% incidence of positive reactors which may be encountered in an unselected population.

As I said, I am making this criticism rather strong on purpose, just to get the greatest possible rise or response out of Dr. Drake and maybe Dr. Stokes.

DR. MILES E. DRAKE, Philadelphia: I wish to thank Dr. Sabin and Dr. Hsia for their comments. In answer to Dr. Hsia's question, I have not skin tested infants under 6 months of age with hepatitis. Among 500 infants we have observed in the last two or three years in large epidemics, we have seen only 2 with jaundice, one aged 4 and one aged 7 months. Thus, on the basis of our criterion of jaundice, we would not have tested many such children. However, we have tested supposedly normal children and found that under one year of age probably 1 to 2% have a positive skin reaction.

In answer to the second question—have we skin tested infants of mothers who had infectious hepatitis during pregnancy?—we have not made a study of this problem. We have, however,

skin tested a number of infants, some 10 or 12 months old, who have had jaundice within the first six to eight weeks of life and who have been shown not to have congenital anomalies or obstruction. We believe they represent cases of transplacental infectious hepatitis, and this belief is based on the transmission of a long-incubation-period hepatitis or serum hepatitis from the blood of the infant and from the blood of the mother. They have all had negative reactions to skin tests.

In answer to Dr. Hsia's third question, regarding immunity, we have not studied that in infants.

Now, as to Dr. Sabin's remarks, we skin tested some 42 children initially, of whom 2 had positive and 39 had negative reactions. One year later we retested some 35 of these children and found that the incidence of skin-test positivity had increased from approximately 8% to 60%. That fact may not be significant; I do not know; I am not a statistician.

As to rechallenging, we have considerable information regarding this in volunteers, and Dr. Stokes, Dr. Henle, and I would agree with Dr. Sabin that we should like much more. Volunteers are difficult to get.

Secondly, we had hoped that we might be able to set up an experiment of the nature described in the institution where we worked. We were unable to do so because it is a mental institution, and certainly the children are not volunteers. We were unable to rechallenge them with active virus.

I am somewhat hestitant about the possible alteration in susceptibility. We do not know exactly what it means. We are presenting it as a possible immunity to infectious hepatitis on the basis of more recent experiments on human volunteers. We hope to throw more light upon this subject. It would appear that the virus has not been completely inactivated, and on the 15th embryonic passage hepatitis developed in one girl, so that we believe the virus is present in the amnionic fluid. These girls never get out of an isolated unit, and they do not come in contact with anyone. We believe that the case was not a fortuitous but an actual one.

Further work is being done in an effort to show whether what Dr. Sabin has pointed out is or is not true. Is this immunity, or is it just a chance observation? I agree with him that statistics may lead one astray. I think Dr. Stokes might like to add something.

DR. JOSEPH STOKES JR., Philadelphia: I think it is worth while mentioning in connection with Dr. Sabin's questions that jaundice has been produced by second passage from persons who had hepatitis without jaundice from the first human passage of infected amniotic fluid. Also, convalescent serum will neutralize the skin test while acute serum will not, which I think is a good indication that hepatitis virus is present in the amniotic fluid used for the skin test.

Utilization of I^{131}-Labeled Casec in the Study of Protein Digestion and Absorption.

DR. PAUL S. LAVIK, DR. LEROY W. MATTHEWS, DR. SAMUEL SPECTOR, and DR. HYMER L. FRIEDELL, Cleveland.

A study of protein digestion and absorption was carried out in nine patients with diseases which did not specifically involve the gastrointestinal tract and in five patients with cystic fibrosis of the pancreas. The experimental procedure was as follows: Each patient received 4 to 10 drops of strong iodine solution every 12 hours during the 24 hours preceding and the 4 days after the test to block the thyroid uptake of I^{131}. The test meal, consisting of an aqueous suspension of nonradioactive casec (1.75 gm. per kilogram of body weight) and I^{131}-labeled casec (1.0 μc per kilogram of body weight) in water, was administered orally in place of breakfast. The dose of I^{131} employed was well below the safety limits approved by the Atomic Energy Commission for use in humans. Blood samples were collected at intervals after the test meal, and the urine and feces were collected separately for three days. All samples were assayed for I^{131}.

When the test meal was given to the patients with cystic fibrosis of the pancreas, an average of 22.5% of the administered I^{131} was excreted in the feces. This amount is in marked contrast to the corresponding values obtained for the control patients, which averaged 3% and did not exceed 6%. Administration of pancreatin with the test meal reduced the fecal excretion of I^{131} to an average of 15% in the children with pancreatic fibrosis. If the protein of the test meal was hydrolyzed with pancreatin before administration, the fecal excretion of I^{131} was similar to that found in the controls. Thus, by fecal analysis it was possible to demonstrate an impaired

utilization of protein which was due to a failure in protein digestion. Although the isotope content of the blood and urine rose more slowly in children with cystic fibrosis of the pancreas than in control patients, the difference was not striking.

The rationale of the method described is based on the fact that the isotope in the I^{131}-labeled casec is firmly bound to certain amino acids in the molecule and remains attached to these amino acids during the process of digestion and absorption. In vitro experiments have shown this observation to be true in the dog, and our results support the validity of the method with children.

DISCUSSION

DR. HARRY SHWACHMAN, Boston: You have just seen a neat method of studying protein digestion and its application as a diagnostic tool for study of pancreatic function. In the past extensive studies have ben made with the absorption method so far as fats and carbohydrates were concerned. It is hoped that the addition of this technique will aid us in a better understanding of the derangements of protein digestion.

One of the findings I should like to emphasize is the lack of an absolute or sharp differentiation between normal children and those with presumably complete absence of pancreatic enzymes. Perhaps a variety of proteolytic enzymes are involved, and we in the clinical laboratory rely upon only one and incorrectly say there is a lack of proteolytic activity on this basis. The failure of this test as a dignostic one does not detract from its value as a method of study.

I have one question in regard to the use of pancreatin. Did you also use a pure trypsin preparation and compare the effects?

One of the practical applications of this work is the additional light it throws on the value of pancreatin in therapy. You have shown it to be worth while. Why two patients failed to respond, I do not know. I do not believe the failure was due to inadequate dosage.

So far as amino acid absorption is concerned, all the evidence points to a normal absorption in patients with pancreatic fibrosis. We have used casec in studying protein digestion and find it less suitable than gelatin if we measure the rise in plasma aminoacetic acid. However, unpublished studies with B. S. Gould indicate that casec may be a useful substance provided the rise in level of blood or plasma proline and hydroxyproline is used as a measure of digestion.

Induction of New Type Specificity of Neisseria Meningitidis by Desoxyribonucleic-Acid-Containing Extracts. DR. HATTIE E. ALEXANDER and DR. WINIFRED REDMAN, New York.

Demonstration that highly specific desoxyribonucleic acids function as genes in two different bacterial families, Diplococcus pneumoniae and Hemophilus influenzae, raises the probability that a similar mechanism directs the inherited characteristics of all micro-organisms. This question has become important because of the possible implication that a principle so broad in its application in microbiology may operate in cells of higher species. It is therefore of interest that the inherited traits of another bacterial family have been demonstrated to be controlled by desoxyribonucleic-acid-containing extracts. This paper outlines the results of experiments which show that in Neisseria meningitidis (meningococcus), desoxyribonucleic-acid-containing extracts function as genes.

R-cells derived from Type 2a N. meningitidis by selection of spontaneously appearing mutants have been transformed with predictable regularity into Type 1 N. meningitidis by exposure to a desoxyribonucleic-acid-containing extract isolated from Type 1 N. meningitidis. The process which brings about this change in inherited characteristics occurs almost instantaneously. As in the H. influenzae system, only a minute proportion of the total population exposed is susceptible to this change. The transforming activity can be destroyed within five minutes by exposure of the desoxyribonucleic-acid-containing extract to appropriate concentration of crystalline desoxyribonuclease.

The data suggest that type specificity and virulence of meningococci are controlled by highly specific desoxyribonucleic acids. It is suggested that under suitable stimuli, the phenomena described in vitro may play a role in epidemics of meningitis.

DISCUSSION

DR. HORACE L. HODES, New York: I should like to ask Dr. Alexander if she has ever made any attempt to correlate the ability of the organism to change with alterations in resistance to antibiotics.

DR. EDWARD C. CURNEN, New Haven Conn.: I should like to express admiration for the experiments which Dr. Alexander has described. I should also like to inquire whether, with the transformation of an organism from one type to another, the characteristics of virulence are retained from the old type or acquired from the new one.

DR. HATTIE E. ALEXANDER, New York: We have not made any studies in the N. meningitidis system to explore the correlation between type specificity and virulence. On the other hand, work which has been done in the pneumococcus system shows a very close relationship between the amount of polysaccharide elaborated, for example, and virulence, and I believe this principle will apply to H. influenzae.

To answer Dr. Hodes, we have not explored the trait of resistance to antibiotics in the N. meningitidis system, but perhaps he was trying to bring out the fact that this particular trait, resistance to antibiotics, which is an inherited one in the pneumococcus system, has been induced by highly specific desoxyribonucleic acid isolated from pneumococci resistant to penicillin. This trait is transformed or induced independently of the type-specific trait.

Effects of Posterior Pituitary Extracts on Electrolyte Metabolism. DR. ROSE G. AMES and DR. H. B. VAN DYKE, New York.

The action of the antidiuretic hormone, secreted by the neurohypophysis, on the renal tube reabsorption of water is well substantiated. Its normal participation in electrolyte excretion is controversial. Variable results have been obtained by numerous investigators. The dose of hormone and the different species used in the experiments have been thought to be responsible.

A preparation of pure oxytocic principle prepared by Vincent du Vigneaud at Cornell University medical School had no apparent effect on the electrolytes studied. A special preparation of antidiuretic principle (Parke, Davis & Company) which was extremely low in oxytocic activity and an apparently pure protein extracted from the posterior lobe of bovine pituitaries according to the method of van Dyke and associates were the antidiuretic substances used in the experiments reported herein. With physiologically active doses of antidiuretic hormone we also observed variable effects on the urinary excretion of electrolytes in normal dogs and dogs with diabetes insipidus in varying states of hydration. However, when an increased electrolyte load was induced by infusing sodium chloride solutions the results were consistent. The hormone was infused at the rate of 10 to 15 mμ in 45 to 60 minutes, or single injections of 1 to 5 mμ were given in the course of the experiments. Creatinine and *p*-aminohippurate clearances were measured concurrently. In every experiment a definite increase in the amount of electrolyte excreted was observed during the period of hormone administration as compared with control periods before and after such administration. The increment in electrolyte excretion was correlated with the excretion rate prior to hormone administration. The rate of sodium excretion approximately doubled itself under the influence of the hormone up to the level of approximately 700 μEq. (microequivalents) a minute, at which rate the increment fell off rapidly and approached zero at over 1,000 μEq. a minute. The dose of hormone had little effect on this action.

These experiments were carried out in normal dogs and dogs with diabetes insipidus, in intact rats under alcohol anesthesia, and in one patient with diabetes insipidus.

DISCUSSION

DR. HENRY L. BARNETT, New York: I think this very beautiful paper helps to explain the discrepancy in previous results concerning the effect of the antidiuretic hormone on electrolyte excretion. I should like to add that similar results have recently been obtained in Dr. Pitt's laboratory at Cornell.

DR. NATHAN B. TALBOT, Boston: I want to add my word of appreciation for this further clarification of a complex problem. I should just like to ask the authors one question, namely, do they feel convinced that the agent used was pure antidiuretic hormone? For a number of years

we thought we were dealing with pure insulin and then discovered that the crystals of pure insulin contained a substance with effects diametrically opposite to those of insulin itself. In other words, we have come to realize that many glandular extracts are far from pure as we obtain them. What I am driving at, of course, is that the sodium effects seen in these experiments may perhaps have been due to a contaminant present in the antidiuretic-hormone preparation.

DR. ROBERT COOKE, New Haven, Conn.: I should like to emphasize the point that Dr. Talbot made. We have studied a condition of posterior pituitary release from the individual's own pituitary, namely, heat stress, in which there is associated water deprivation. Under this condition there is actually an increased reabsorption of electrolyte. It is perfectly possible that in our experiments there was some increase in the adrenal cortex hormone output, but if there was very much effect coming from the individual's own pituitary, it was markedly overshadowed by the retaining effect of some other circulating principle.

DR. ROSE G. AMES, New York: Dr. Talbot, we have used various extracts of the posterior pituitary. The vasopressin injection (pitressin®) we used was a special preparation from Parke, Davis & Company that had an extremely low oxytocic action. The pure protein I mentioned is one that has been isolated by Dr. van Dyke from posterior lobes of bovine pituitaries and has the qualities and characteristics of a pure protein, and the actions are in the same ratio as the dried U.S.P.-standard powder. We have also obtained from Dr. du Vigneaud pure oxytocic principle, which contains only eight amino acids and is a very small molecule. Dr. van Dyke and I feel that this is probably the active part of the hormone molecule. This preparation had minimal antidiuretic action.

As far as Dr. Cooke's question goes, we have thirsted dogs and observed their sodium excretion after antidiuretic-hormone administration. Their sodium excretion is very low. The dogs have diabetes insipidus and they lose about 3 kg. under this regimen.

When the excretion of sodium is high enough in the thirsted dogs, we get an increase in sodium excretion. These results have been variable.

Our intact dogs were made extremely uncomfortable during one of our experiments; an antidiuresis occurred and the sodium excretion more than doubled.

Variability in Erythroblastosis Fetalis: A Study of Multiple Pregnancies and of Twins. DR. VICTOR C. VAUGHAN III, New Haven, Conn., and DR. FRED H. ALLEN JR. and DR. LOUIS K. DIAMOND, Boston.

In the course of studies of erythroblastosis fetalis previously reported to this society, we became much impressed with the frequent occurrence of unexpected good or bad results in a number of families in which more than one or two erythroblastotic infants had been born. We should like to present here the results of a study of family patterns of disease in 24 mothers, all Rh-negative and sensitized, each of whom has given birth to four or more infants with erythroblastosis fetalis, to the number of 141 affected babies in all. The 24 mothers form two groups: first, an obstetrical group of 12 mothers delivered at the Boston Lying-in Hospital or the Grace-New Haven Community Hospital and, second, a pediatric group of 12 mothers, each of whom was delivered at some time of an infant who was transferred from another hospital to the Children's Medical Center, Boston, or the Grace-New Haven Community Hospital for treatment.

The obstetrical group of mothers were delivered of 69 infants, of whom 29 (42%) were stillborn, with a mortality of 50% for 40 live-born infants. The pediatric group of mothers were delivered of 72 babies, of whom 19 (26%) were stillborn, with a mortality of 40% among 53 live-born infants. The difference in mortality in live-born infants does not attain statistical significance, but the difference in stillbirth rate between the two groups is significant. Since exchange transfusion was available for very few of the live-born infants, we have no reason to feel that treatment modified the results in these babies to a major degree, except as certain babies may have been subjected to a high risk of kernicterus through the early induction of labor in the sensitized mother.

We have been unable to demonstrate in these families a uniform tendency to worsening of erythroblastosis fetalis in successive pregnancies after the first affected infant, as indicated in Table 1. On the other hand, there is a strong tendency (P is less than 0.01) for infants who

recovered to be found in those families in which the first affected infant recovered and for stillborn infants to be found in those families where the first affected infant was stillborn. These tendencies are shown in Table 2, which also shows a less conspicuous trend to the occurrence of neonatal deaths in those families where the first affected infant died in the neonatal period. The second, third, or fourth affected infant can also be shown to be a good index of family trend toward recovery or death of affected infants.

These results seem to establish the existence of family patterns of disease which result not infrequently in the occurrence of many recoveries in a given family or, in another family, in regular occurrence of stillbirths. Within this general framework of family patterns, there is often capricious variability, such as that evidenced by the experience of a mother whose first infant was mildly affected, whose second died of kernicterus, whose third recovered from severe erythroblastosis fetalis, whose fourth was stillborn with profound hydrops at 32 weeks' gestation, whose fifth was delivered at term with mild illness, and whose sixth was born at 28 weeks with profound hydrops. At least 6 of the 24 families may be considered to show conspicuous variability.

TABLE 1.—*Outcome in Successive Pregnancies—Twenty-Four Families*

Baby	Recovered, %	Kernicterus,* %	Died, 1st Day,† %	Stillborn, %	No. of Cases
1st affected	42	21	8	29	24
2d affected	46	13	21	21	24
3d affected	28	12	16	44	25 ‡
Subsequent	35	15	12	38	68
Total	37	15	13	35	141

* Includes all deaths after the first day and before the seventh day when kernicterus was proved or seemed likely from clinical signs or from time of death.

† Includes one death in the neonatal period after the first day, due to erythroblastosis fetalis, when kernicterus was not present.

‡ Kernicterus developed in one set of dizygous twins.

TABLE 2.—*Outcome in Relation to Result in First Affected Infant*

Result in First Affected Infant	No. of Cases	Outcome in Subsequent Infants			
		Recovery	Kernicterus *	Died, 1st Day *	Stillborn
Recovery	10	24	3	8	9
Kernicterus *	5	10	7	5	11
Died, 1st day	2	3	4	1	1
Stillborn	7	5	3	3	20

* See footnotes to Table 1.

We do not know why erythroblastosis fetalis assumes characteristic forms in certain families with sometimes monotonous regularity, or why departures from family trends occur. But that some variability is inherent in the infant is strongly suggested by our experience with 21 sets of Rh-positive twins. Of these 21 pairs, 9 showed conspicuous difference in severity of illness at birth between members of the pairs, in spite of exposure to the same type and titer of maternal antibody and the same general intrauterine milieu. These differences were definitely more likely to be found among the 12 twin pairs known to be dizygous. Only one of the other nine pairs showed a considerable difference in clinical severity, whereas eight of the dizygous pairs did so. This observation suggests that genetic factors may be important.

The major inference to be drawn from this study of family trends and variability in erythroblastosis fetalis is that it is hazardous to offer absolute predictions of the outcome of erythroblastosis before delivery, and it may also be inferred that there is no history so bad that good results may not chance to happen in another pregnancy. We would caution strongly against drawing conclusions as to family trends from fewer than two or three affected infants.

Cerebral Blood Flow Determinations in Infants and Children. DR. J. M. GARFUNKEL, DR. H. W. BAIRD, and DR. H. T. WYCIS, Philadelphia.

The nitrous oxide method for the measurement of cerebral blood flow, as devised by Kety, has been found to be useful in adults. The method is not practical, however, for infants and small children, since 70 to 100 cc. of blood is required for the determination. By employing the method of Scholander for gas analysis, in which very small amounts of blood are required, we have found that the principles outlined by Kety are applicable for the determination of cerebral blood flow in infants and children. The modified method has been found to give reproducible results and to be practical and safe, even for young infants.

The nitrous oxide method, as described by Kety, depends upon these assumptions: (1) that nitrous oxide in the low concentrations used is physiologically inert; (2) that within 10 minutes equilibrium is reached between blood and brain, so that the solubility ratio between blood and brain equals 1; (3) that blood from either internal jugular bulb is representative of mixed cerebral venous blood. Some investigators question the last point, but the consensus is that in the great majority of persons blood from one internal jugular vein at the level of the superior bulb is fairly representative of mixed cerebral blood. This opinion has been borne out in the two patients from whom we have taken samples simultaneously from each side. It has also been demonstrated that the amount of contamination by blood from extracerebral sources at the level of the internal jugular bulb is not significant.

Samples of blood are withdrawn from the arterial and the cerebral venous circulation at intervals after the patient begins breathing a nitrous oxide-oxygen mixture. The levels of nitrous oxide measured in these samples are plotted against the time of their withdrawal, and the points on the graph may be connected to form arterial and venous curves of nitrous oxide content. The area between the arterial and venous curves is a function of the cerebral blood flow during the time of sampling. As shown by Kety, this relation may be expressed by the equation:

$$\text{C.B.F.} = 100\ V_t S \int_0^t (A\text{-}V)dt = \text{cc./100 gm./min.}$$

where V_t is the nitrous oxide content of cerebral venous blood when in equilibrium with brain tissue,

S is the distribution ration of nitrous oxide between blood and brain,

$\int_0^t (A\text{-}V)dt$ is the integral of the arteriovenous difference of nitrous oxide in vol.% from onset of inhalation (o) to equilibrium time (t), which is 10 minutes.

After the patient is given sedation and restrained, a No. 20 needle is inserted in the internal jugular bulb and is kept open by a slow drip of saline solution by way of a three-way stopcock. A No. 20 Murphy-Gardner type needle is then inserted in a femoral artery. It is kept patent by injecting heparin solution to fill the system and then closing the stopcock. While these procedures are in progress, and for a total of 20 to 30 minutes, the patient inhales 100% oxygen to wash excess nitrogen from the blood. Initial arterial and venous samples are taken. The subject then breathes a mixture of 20% nitrous oxide and 80% oxygen for 10 minutes. Because of the necessity for a smooth inhalation curve, heavy sedation must be employed. Recently, rectally administered secobarbital (seconal®) and small doses of intravenously administered thiopental sodium (pentothal sodium®) have been used. Unfortunately, barbiturate anesthesia is known to have a depressant effect on cerebral circulation and cerebral oxygen consumption, and there appears to be no way of obviating this difficulty in the young uncooperative patient. Analgesic rather than anesthetic doses are used. Five serial arterial and venous samples are drawn at accurately timed intervals during the 10-minute period of gas inhalation. Specimens are taken more frequently during the first four minutes, when the blood content of nitrous oxide is changing rapidly. A 1-cc. sample is adequate for five or six determinations. Results are reproducible within 0.1 vol.%. Scholander has shown that this method of analysis is accurate when compared with the method of Peters and Van Slyke, which requires much larger volumes of blood. Without increasing the amount of blood drawn, oxygen determinations are also possible, though in our laboratory these determinations have been less consistently accurate than the nitrous oxide analysis.

Satisfactory determinations have been made on 15 infants and children who ranged in age from 4 weeks to 7 years, 9 of whom were less than 2 years old. Normal children have not been studied. The clinical diagnoses for the patients studied included hydrocephalus (seven cases), spastic quadriplegia (four cases), mental retardation (one case), hemihypertrophy (one case), hypothyroidism (one case), and microcephaly (one case).

Of the hydrocephalic patients, the five who were markedly retarded mentally and physically had reduced cerebral blood flow by normal adult standards. One 10-month-old infant and one 6-year-old child, whose development was considered to be average for age, had normal curves. One infant was studied before and after a lumbar subarachnoid-peritoneal shunt procedure. Although there was clinical improvement, no significant increase in cerebral blood flow was demonstrable one week postoperatively.

In conclusion, an adaptation of the Kety nitrous oxide method for the determination of cerebral blood flow has been shown to be practical and safe in infants and children. Preliminary observations suggest, but do not establish, that there are significant changes in cerebral blood flow in hydrocephalic patients who are mentally and physically retarded. Further studies are in progress to determine cerebral blood flow in a variety of neurologic conditions and, when possible, before and after neurosurgical procedures.

DISCUSSION

DR. CHARLES KENNEDY, Philadelphia: Modification of the nitrous oxide method for measuring cerebral circulation promises to open up a wide field of investigation in pediatrics. However, I was rather puzzled that oxygen was used prior to the administration of nitrous oxide.

If I remember correctly Kety has shown that pure oxygen reduces blood flow by about 35%, and I should like to know if the investigators feel that its use had an effect on the measurement of cerebral blood flow.

I was also interested in the shape of the curves shown in the child with cerebellar atresia where it appeared that the arterial and venous curves did not level off. We have interpreted this type of curve as indicating significant extracerebral contamination. I wonder if I could be informed on that point.

DR. JOSEPH M. GARFUNKEL, Philadelphia: In answer to Dr. Kennedy's question regarding the use of oxygen prior to the determination, we are aware that a decrease of about 13% in cerebral blood flow has been reported by Kety as a result of the administration of high concentrations of oxygen. However, Dr. Nims found that when 100% oxygen is given, a decrease in cerebral oxygen uptake occurs without any effect on cerebral blood flow. Dr. Schmidt has also stated that any change in cerebral blood flow from the use of oxygen in this way would not be significant.

In answer to Dr. Kennedy's question regarding the rising arterial curve, we believe that this may be explained by an increasing concentration of nitrous oxide during the gas administration. We have therefore discontinued the use of an anesthesia machine for the administration of the gas and use instead a Douglas bag.

In answer to a question raised by Dr. Hodes as to the effects of anesthesia on cerebral blood flow, we have tried to use sedative rather than anesthetic doses. A smooth inhalation curve is essential, and sedation must be employed to achieve this. Some of our subjects had inadequate sedation, and the resulting curves were irregular and had to be discarded. With deep surgical anesthesia there is first a decrease in cerebral oxygen consumption and finally a lowering of the cerebral blood flow. We feel that the anesthetic agents we employed had little or no effect on cerebral blood flow.

Creatine Excretion in Premature Infants. STANLEY COHEN, PH.D., DR. ROBERT G. FRAZIER, and DR. HARRY H. GORDON (Denver).

An attempt has been made to clarify the mechanism accounting for the urinary excretion of less creatine by the premature than by the full-term infant. Studies were made of the effect of feeding creatine and creatine precursors on the excretion of creatine, creatinine, and guanidoacetic acid by these infants. Blood levels of creatine and creatinine were determined in relation to urinary excretion. Analyses also were made of the creatine content of the rectus muscle during various stages of fetal development.

The oral administration to five premature infants of an equimolecular mixture of arginine, aminoacetic acid, and methionine equivalent to one-fourth the dietary nitrogen produced no

increase in excretion of creatine. This observation indicates that the dietary supply of these amino acid precursors of creatine was not the limiting factor determining the low creatine excretion.

Both premature and full-term infants excrete guanidoacetic acid, and they do so in comparable amounts. Feeding a mixture of arginine and aminoacetic acid to one full-term infant and four premature infants caused a slight and similar increase in guanidoacetic acid excretion, a fact which does not suggest any inability of the premature infant to synthesize guanidoacetic acid.

When a single dose of a mixture of guanidoacetic acid and methionine was fed to four premature and two full-term infants they responded by an increased excretion of guanidoacetic acid during the first 24 hours. Creatine excretion was also increased and remained so for at least three days. The increased urinary excretion of both these substances was much more marked in the full-term than in the premature infants. This observation again indicates no lack of precursors of creatine in the premature infant and does not necessarily suggest any inability of the premature infant to synthesize creatine, since the amount excreted may also be influenced by storage and renal function.

The oral administration of a single standard dose of creatine, calculated on the basis of surface area, resulted in the excretion of 35 to 50% of the ingested dose in three days by five premature infants, as compared with 70 to 80% by two full-term infants. From these data it was concluded that in the premature infant the tissues had a greater avidity for creatine, or renal excretion was less, or both.

Biopsy specimens of muscle were obtained from 19 infants who were born dead or died shortly after birth. The creatine content of muscle increased from an average of 170 mg. per 100 gm. of wet weight in three infants weighing 500 to 750 gm. to an average of 240 mg. per 100 gm. in two infants weighing between 3,000 and 3,500 gm.

In 28 premature infants ranging from 6 to 92 days of age, the average serum creatine level was 0.76 mg. per 100 ml. The average creatinine clearance was 40 cc. a minute per 1.73 square meters. In two older full-term infants creatinine clearances of 91 and 110 cc. a minute per 1.73 square meters and serum creatine levels of 0.83 and 0.69 mg. per 100 ml., respectively, were obtained. If the difference in filtration rate, as measured by the creatinine clearance, were the sole limiting factor, one would expect the serum creatine of the premature infant to be higher than that of the full-term infant. Since this is not the case, one must presume that increased storage or decreased synthesis is also present in the premature infant. We obtained no evidence for decreased synthesis of creatine in the premature infant, and since the recovery of creatine in the tolerance test was also low this observation suggests that the premature infant has increased capacity to store creatine. This finding is in agreement with the data from the muscle biopsies.

No evidence was found that either diminished rates of synthesis, if they were present, or decreased creatinine clearances, which were present in the premature infants, were acting as limiting factors. These data are in agreement with the hypothesis that the premature infant excretes less creatine than the full-term infant because of a greater capacity to store creatine.

DISCUSSION

DR. HARRY H. GORDON, Baltimore: It is obvious that Drs. Frazier and Cohen have done a large amount of work and have produced information consistent with a hypothesis rather than direct evidence.

Some of you may remember that last year Drs. Nitowsky and Puck presented estimates of I^{131} storage by the thyroid that were derived from mathematical analysis of urinary excretion. The method of analysis made their estimates independent of diminished renal function, and it may be that if isotopically labeled cratine were fed to premature and full-term babies, a similar analysis of the data would produce more direct evidence on storage.

Finally, it is worth mentioning the paradox that premature infants and adults have no or very little creatine in their urine, while full-term infants excrete large amounts.

DR. HENRY L. BARNETT, New York: I know Dr. Frazier has considered but perhaps did not get time to discuss the possibility that aminoacetic acid has a direct competitive effect on tubular reabsorption of creatine. Such a possibility complicates somewhat the interpretation of studies using creatine excretion to estimate utilization of aminoacetic acid to form creatine.

I should like to ask if it was possible to calculate creatine clearances during the creatine-tolerance tests and if so if the clearances increased to the values for the full-term infants.

DR. ROBERT G. FRAZIER, Denver: I should like to thank Dr. Gordon for his comments. As far as Dr. Barnett's question is concerned, we do have some reservations about the interpretation of the data because of the known fact that several substances compete with creatine for reabsorption in the renal tubules. These substances include aminoacetic acid, arginine, and possibly guanidoacetic acid. In the experiment in which arginine and aminoacetic acid were fed, the increase was only in guanidoacetic-acid excretion, with no increase in the excretion of creatine. We have only indirect evidence that glycine and guanidoacetic acid compete with each other for tubular reabsorption. It is therefore a little hard to answer the question as to whether the concurrent excretion of glycine produced any increase in the excretion of guanidoacetic acid. This would seem an unlikely possibility since no increase in creatine excretion occurred. I think the work of Pitts showed that it took high serum levels of aminoacetic acid to block the reabsorption of creatine.

We thought of trying to measure creatine clearance during the height of the blood level following creatine administration. We were hampered somewhat by the method, which requires about 5 cc. of blood for the determination of serum creatine and creatinine. We hesitated to draw from these infants more than two or three samples at most and preferred to draw only one in that short period. On a few occasions when we did measure serum creatine levels, they were markedly elevated, but we have no accurate data on the creatine clearances at these times.

Studies of Body-Water Distribution in Normal Infants and in Infants During Dehydration and Subsequent Recovery. DR. AVRUM LABE KATCHER, DR. MARVIN F. LEVITT, DR. AVRON Y. SWEET, and DR. HORACE L. HODES, New York.

The therapy of infantile diarrhea has consisted of parenteral administration of salt, plasma, water, and base. Specific amounts have been calculated from estimated deficits in extracellular water and salt plus prejudged minimal daily requirements. That coexistent deficits of intracellular fluid and electrolytes exist and require therapy has been demonstrated more recently. The development of methods for the in vivo estimation of extracellular volume and total body water has permitted us to attempt the serial measurement of these volumes and renal function during the stage of dehydration and during subsequent recovery.

For this study, the two-hour in vivo volume of distribution of deuterium oxide has been used as a measure of total body water. The volume of distribution of inulin has been calculated as a measure of extracellular volume. Volume of distribution of Evans blue (T-1824) has been utilized as an index of plasma volume. These measurements were performed on normal infants 6 weeks to 8 months of age who were in ostensible homeostasis.

Total body water, expressed as volume of distribution of deuterium oxide, was studied in 10 infants. Volumes ranged from 550 to 710 cc. per kilogram of body weight. The mean was 620 cc. per kilogram. The standard deviation of the mean was 53 cc. per kilogram. Volume of distribution of inulin averaged 265 cc. per kilogram in 18 infants with a standard deviation of 24 cc. per kilogram. Plasma volume in 10 infants reached a mean of 58 cc. per kilogram with a standard deviation of 7 cc. per kilogram. The noninulin body water, a first approximation of intracellular-fluid volume, obtained by subtraction of volume of distribution of inulin from total body water, was 366 cc. per kilogram with a standard deviation of 64 cc. per kilogram in six infants.

Seven infants were studied during acute dehydration due to diarrhea and vomiting and during subsequent convalescence. The infants all showed on admission reduction in the inulin space and in total body water. Intracellular water at the time of admission was decreased in some instances and in others was within the normal range of values.

Infants were treated by intravenous administration of hypotonic fluids. Sicker infants received blood or plasma infusion. Sodium lactate was administered for correction of the metabolic acidosis, and subsequently hypotonic saline solutions with glucose were supplied. The regimen was that customarily used in the pediatric service of the Mount Sinai Hospital and was conducted by the ward staff not engaged in this study. On this standard regimen, all infants studied showed during the early recovery period a striking increment of the volume of distribution of inulin to values well above their own subsequently determined normal value.

This increment was somewhat greater than changes in total body water or body weight. The increment was seen as early as two days and as late as two weeks after commencement of therapy. It persisted beyond discontinuance of parenteral fluid therapy.

The total body water during recovery speedily regained its normal volume and in most instances remained relatively constant thereafter. It should be noted that changes in body weight did not closely parallel changes in total body water or volume of distribution of inulin during this period. The intracellular water did not expand during the early phase of recovery. In some cases it suffered further decrement. It did not return to control volumes for 10 days to 2 weeks. Plasma volume failed to show striking change during the recovery period. The small changes observed correlated qualitatively with changes in the inulin space.

Two illustrative cases were reported, and slides were shown in which changes in the volumes of distribution were graphed as percentage variations from subsequently determined normal values for that infant, as liters.

Infant R. A. showed the usual increment in inulin space at the end of one week of therapy —the infant had not been receiving fluids intravenously for two days at this time—and the corresponding failure of the total body water or weight to equal this rise quantitatively. The noninulin water, accordingly, during this first period, was lower than the values subsequently obtained after recovery. There was a tendency for clearances of inulin and *p*-aminohippurate to change in direction of volume of distribution of inulin. Recovery to normal values was complete in two weeks. Body weight did not parallel the changes in total body water.

Infant M. J. showed one of the most marked increments in inulin space. On clinical grounds she was considered to be severely ill. She had some reduction in clearance of inulin and *p*-aminohippurate on admission. The magnitude of the change in inulin space was greater than the amount of isotonic solution of sodium chloride administered. Body weight was not altered as strikingly. Changes persisted at last three days after discontinuance of parenteral therapy.

In summary: 1. Normal values for total body water and inulin water in infants from 6 weeks to 8 months of age are presented.

2. Infants during recovery from dehydration due to vomiting and diarrhea showed a striking increase in volume of distribution of inulin during the first 3 to 14 days. The fact that this increase was not accompanied by a compatible increase in total body water indicates that noninulin water fails to return to normal and may even be further reduced during this period.

3. Body-fluid distribution does not return to normal until some time after parenteral therapy is discontinued and normal diet is resumed.

DISCUSSION

DR. NATHAN B. TALBOT, Boston: I should like to ask for more information about the quantities of sodium administered to these patients. Was sodium increased appreciably above their average normal intake of probably about 70 mEq. per square meter a day? Especially in patients with stress-induced hyperadrenocorticism an increase in sodium intake is apt to result in abnormal sodium retention and edema formation. I am also curious to know whether these patients were given potassium and if so what relation the institution of potassium treatment bore to the patient's course.

DR. HENRY L. BARNETT, New York: I am impressed with the large expansion of the inulin space persisting for such a long time in these infants, and I am trying to figure out what this means in terms of whether inulin or chloride can be used to estimate extracellular-fluid space. I think my major contribution to this discussion might be to encourage some of the people from New Haven, Conn., or Boston to comment on the results.

I should like to inquire about a technical point concerning measurement of the inulin space. What method was used to obtain equilibrium and how long was the period of equilibrium extended, particularly in the severely ill infants?

DR. DANIEL C. DARROW, New Haven, Conn.: If I understood correctly, the paper reported that the expansion of water did not follow the changes in body weight. For this reason, a discussion of the paper must consider the possible errors of the methods. First of all I should like to state that I have avoided determinations of extracellular volume because of the probable great errors involved. I have always used the extracellular position of chloride with reservation, assuming that the changes in body chloride involved only the extracellular chloride but realizing that considerable chloride is intracellular and may also vary.

Extracellular fluid is obviously a heterogenous phase of total body water in which it is not certain that any natural constituent or material administered is distributed at a uniform concentration in all parts of the water outside the cells. I am exceedingly skeptical of any measurement of extracellular water based on the distribution of inulin. The difficulties appear in the recent paper in the *Journal of Clinical Investigation* by Dr. Homer Smith and a co-worker. If the inulin space is equal to total extracellular water, their data indicate that the average concentration of chloride in cell water is 25 mEq. per liter. In adults, muscle-cell water constitutes about 70% of total intracellular water and contains no more than 12 mEq. per liter, which would indicate that the cellular fluid exclusive of that in muscle contains chloride at an incredibly high concentration. Furthermore, their variations in inulin space are much wider than are likely in normal persons for extracellular water.

I think, therefore, that the inulin space measures some part of extracellular water. It may measure the readily available extracellular space. In regard to the paper under discussion, I suggest that in the expansion of extracellular space with sodium chloride the readily available proportion of extracellular space is expanded and measured by changes in inulin space. I do not believe total extracellular space is correspondingly expanded.

As to the deuterium oxide measurement of total water, I have always regarded the method as fundamentally sound. It is disappointing to become skeptical of this method. I am not a bit skeptical of the ability of these men to use the method. But it is obvious that if the body weight does not follow closely the total body water we have to account for changes in solids in quantities that are impossible.

And so I think we have to become skeptical of the deuterium-oxide method—at least as it can be carried out in severely sick infants. And how can we escape the difficulties and assumptions of balances if we cannot determine the water of the body?

DR. AVRUM LABE KATCHER, New York: I wish to thank Dr. Talbot, Dr. Barnett, Dr. Darrow and Dr. Weech for their comments and questions.

In answer to Dr. Talbot's question concerning the amount of sodium which was administered to the infants studied, I might use as an illustration the second case I reported. The total amount of salt given that infant prior to the second determination of body-fluid distribution represented 120 to 130 mM. of sodium and somewhat less of chloride. The absolute magnitude of the change observed in the volume of distribution of inulin was slightly greater than the total amount of sodium, expressed as milliliters of isotonic sodium chloride solution, which was administered.

The over-all change in total body water was so much less than the change in the volume of distribution of inulin that, while the mechanism which Dr. Talbot mentioned certainly was operating, there must have been another factor as well, namely, a shift of fluid out of the cells.

In answer to the question about potassium, the staff in the ward who were conducting the management of these infants administered potassium chloride to two of them, starting on the second day of treatment. About 5 to 8 mM. per kilogram of body weight a day was given by mouth. Although the changes in these two infants were quantitatively less marked than in the others, both infants showed exactly the same changes in exactly the same directions and their cases fitted perfectly with the others studied.

In answer to Dr. Barnett's question, in all cases we measured the volume of distribution of inulin by the collection of urine after a six-hour equilibrium period of inulin given intravenously at a constant rate. We demonstrated in normal infants, dehydrated infants, and infants recovering from diarrhea that equilibration could take place in less than four hours after the continuous intravenous infusion was started. We used as a minimum equilibration period six hours. Prolongation of the period of equilibration beyond four hours produced no increase in the volume of distribution of inulin.

In one or two cases we also measured the space by the method of differences. The results checked moderately well, and we were able to show that equilibration must have taken place in three to four hours. Collections of urine were prolonged for 12 to 18 hours, and we found that all the inulin given intravenously was excreted by them.

At the time of the initial study of a dehydrated baby, the amount of fluids given during the six-hour period of equilibration was in no case more than 30 ml. an hour and in most cases was 15 ml. an hour. It is hard to believe that this amount of fluid could have altered the results.

The infants were not treated during the initial period of study. All data needed were accumulated before the end of the six-hour period, including the various blood chemistry determinations, and as soon as equilibration of inulin was complete the ward staff proceeded with the hydration of the infants according to their customary plan of therapy. Once the equilibrating infusion is over, of course, one no longer need care about the amount of water put into the child as far as this study is concerned.

With regard to Dr. Darrow's questions and observations, I agree with Dr. Hodes. I would rather not enter into a discussion between Dr. Darrow and Dr. Smith.

We do not pretend that our methods are error-proof. We do not believe that the volume of distribution of inulin is an exact representation of the extracelluiar fluid volume. We know, for example, that inulin does not penetrate the cerebrospinal fluid. We use the volume of distribution of inulin as an approximation of the fluid, or active, phase of the extracellular compartment. The reliability of this concept is enhanced by the observation that four infants showing marked increase in volume of distribution of inulin became clinically edematous.

With regard to the point about relationship of total body water and body weight, Dr. Weech pointed out one obvious source of error, namely, that we used the usual ward scales, which are subject to error. Body weight did not closely parallel fluctuations observed in the total body water. I will not venture an explanation of that observation.

Dr. Weech asked a question about the mean and the spread in the data on normal volumes of distribution of inulin. Those figures were thrown off slightly by two infants, who had, respectively, spaces of 310 ml. and 330 ml. per kilogram. We subsequently noticed that both infants had been studied after respiratory infections. A draining ear developed in one the day after the study was completed. The range was thrown off somewhat by one or two infants at each end. About 15 of the 18 infants were grouped closely about the mean, and we used that fact as a basis for calculation of our standard deviation.

Development of Resistance by Mycobacterium Tuberculosis to Streptomycin, Viomycin, and Paraaminosalicylic Acid. Dr. A. Josiukas, Dr. T. E. Roy, and Dr. Gladys Boyd, Toronto, Canada.

Attempts have been made in vitro with numerous freshly isolated cultures of Mycobacterium tuberculosis to determine the ease and rapidity with which strains will develop resistance to drugs by passage on media containing these drugs.

Passage and sensitivity tests were done on Herrold's egg-yolk agar. For purposes of subculturing from the passage tubes, use was made when possible of large, flat, moderately moist and luxuriant colonies which appeared after the third to fifth week of incubation among the colonies in the marginal inhibitory zone of growth. These "adapted" colonies yielded subcultures usually more resistant than the parent strain.

All cultures were of normal sensitivity to all three drugs initially except when strains of artificially induced resistance were used. None had been exposed previously, as far as could be ascertained, to any of the antibiotics either in vivo or in vitro.

Passage of 55 strains of normal streptomycin sensitivity on streptomycin showed a moderately fast development of resistance, so that after the sixth passage (3 weeks' exposure) all grew in streptomycin concentrations of 100 to over 1,000 γ per cubic centimeter. Passage of 55 strains on paraaminosalicylic acid showed a slow development of resistance, so that after the sixth passage 18 strains remained fully sensitive to paraaminosalicylic acid. In similar passages on viomycin, all of 30 strains became resistant to from 500 to over 1,000 γ per cubic centimeter in a manner comparable to that seen with streptomycin passage. Streptomycin-sensitive and streptomycin-resistant strains were equally susceptible to viomycin and behaved similarly in passages on it.

Passages of strains on combinations of streptomycin and paraaminosalicylic acid showed the effect of paraaminosalicylic acid in delaying or preventing the development of resistance to either the combination or the single drugs. Paraaminosalicylic acid had a similar delaying effect when combined with viomycin in regard to sensitivity to viomycin or to the combination. The dose of paraaminosalicylic acid appeared to influence the rate of emergence of resistant strains. There was a similar synergistic effect between paraaminosalicylic acid and streptomycin and between paraaminosalicylic acid and viomycin.

DISCUSSION

DR. HATTIE E. ALEXANDER, New York: In the discussion of the resistance phenomenon the terminology used suggested two different mechanisms as the explanation for increase in resistance: (1) the "adapted" colony which grew on streptomycin suggests an influence of the antibacterial agent on the organism and (2) the "emergence of resistant strains" suggests a different mechanism.

I should like to bring out the fact that there is no convincing evidence for the first mechanism. On the other hand, there is proof that emergence of resistance in vitro or in vivo is a selective phenomenon. The resistant cell are spontaneously occurring mutants which are merely selected by the antibiotic for survival when the sensitive members are eliminated. The resistant mutants breed true and therefore eventually make up most or all of the population.

Retrolental Fibroplasia in Premature Infants and in Kittens. DR. W. R. HEPNER JR., introduced by DR. A. E. HANSEN, Galveston, Texas.

Blindness due to retrolental fibroplasia is the outstanding complication of survival from extreme prematurity. Although this form of blindness was rare 15 years ago, today it is common, having an average range of incidence of 8 to 24% among infants born weighing less than 1,500 gm.

There is a direct relationship between the degree of prematurity and the incidence of the disease. A similar relationship exists between the degree of prematurity and the severity of physiologic handicaps. Because the incidence of retrolental fibroplasia varies extremely from hospital to hospital, the possibility was entertained that some method of pediatric management might overload the physiologic capacities for adjustment. Consideration was given the differences in electrolyte content of feeding superimposed on the renal incapacities of premature infants, the frequency of edema, and blood transfusion given to infants born weighing less than 1,500 gm., as well as the immature state and rapid growth of the eyes during the first weeks of life.

During a period in which 48 infants were born weighing less than 1,500 gm. and were offered ad libitum only formulae containing 56 mEq. of sodium per liter, 21 became blind from retrolental fibroplasia. Before and after this experience, 103 infants of similar weights were born and were similarly fed formulae containing 20 mEq. or less of sodium per liter; 7 of these 103 became blind from retrolental fibroplasia. Signs of fluid retention in the skin and retinae coexisted in the smaller infants. The retinal signs frequently progressed to hemorrhage, detachment, and fibroplasia in the more immature of the group.

Intravenous blood transfusions are now commonly given to premature infants. Funduscopic examinations of infants with vascular engorgement and retinal edema before and after blood transfusion revealed either retinal detachment or hemorrhage into the vitreous immediately after transfusion in four instances involving six eyes. Dr. Mary C. Fletcher, of Houston, Texas, had a similar experience with one patient and has seen repeated retinal and vitreous hemorrhage during the several days following transfusion in three other patients. Mallek and Spohn of Canada found in retrospect a marked increase in blindness due to retrolental fibroplasia after blood transfusions became common in one of two nurseries in their city. They observed no increase in retrolental fibroplasia in the other nursery.

An attempt was made to duplicate these conditions in the laboratory. Part of each of 12 litters of newborn kittens was made edematous by injections of vasopressin tannate injection (pitressin tannate®) and sodium chloride. After edema was obvious, repeated intravenous blood transfusions were given. Histologic examination of the eyes of the treated animals revealed retinal disease similar to the early retinal stages of retrolental fibroplasia.

After these observations an experiment was begun in three separate hospitals. In each hospital an alternate-patient method was used, controls and treated patients being in weight-paired groups in each hospital. The eyes of premature infants in the units of these hospitals were examined funduscopically at intervals of about two weeks and more frequently when vascular engorgement and tortuosity along with retinal hemorrhages or edema were present. Abnormalities were verified by one or more independent qualified observers, usually ophthalmologists. When retinal detachment or retinal edema with extensive bleeding became apparent, electrolyte starvation with normal caloric intake was instituted. Of 17 infants receiving high sodium formulae (about 56 mEq. per liter), 15 acquired retinal detachment or severe edema

with extensive hemorrhages. The signs in 14 of these 15 affected infants disappeared with "treatment." Of 12 infants receiving normal sodium formulae (about 20 mEq. per liter), 4 acquired retinal disease; in 3 of these 4, also, the disease disappeared with "treatment." Earlier, human milk was tried because of its low electrolyte content. This method most often allowed mild weight loss, with gradual disappearance of edema and the retinal signs of disease. However, the two failures among the 19 affected infants were treated with human milk. Recently, with use of an electrolyte-free formula, the acute changes described disappeared dramatically during a three to five day period. Unfortunately, a time factor seems to be involved. If orbital disorganization was present too long and scar formation established at the time of treatment, the scars remained, even though the signs of vascular engorgement and tortuosity, retinal hemorrhage, vitreous clouding, and increased ocular tension disappeared.

The conclusions which can be drawn from these observations are speculative, and will require for confirmation extensive clinical and laboratory study in widely separate fields. However, it seems justifiable to suggest on the basis of these clinical observations supported by an animal study the following hypothesis: Overloading the metabolic capacities of the more immature premature infants with formulae of greater electrolyte concentration than their ability to manage may lead to the development of increased blood volume, vascular distention, and retinal edema, which may progress to permanent blindness.

The acute disease is made worse by blood transfusion. Remission of the acute disease may be obtained by electrolyte starvation in the presence of normal caloric intake.

Further Observations on Retrolental Fibroplasia, Including Measurements of the Intra-Arterial Blood Pressure in Premature Infants. Dr. W. E. Laupus (by invitation), Dr. H. L. Barnett, Dr. Helen McNamara (by invitation), Dr. E. W. D. Norton (by invitation), and Dr. F. P. Bousquet Jr. (by invitation), New York.

The vascular nature of the earliest eye changes in retrolental fibroplasia led to a consideration of the possible role of hypertension in the causation of this disease. Because of the difficulties encountered by previous investigators in attempting satisfactory indirect blood pressure measurements in premature infants, we undertook direct intra-arterial determinations from the superficial temporal artery or one of its major branches. The Sanborn electromanometer and a direct-writing electrocardiograph were used in recording continuous tracings of instantaneous pressure changes and mean arterial pressures.

The pressure curves obtained were characteristic of similar intra-arterial pressure curves from older persons. In all, 45 measurements were made on 16 infants who ranged in weight from 1.4 to 3.0 kg. and in age from 8 to 64 days at the time of determination. All were at rest or were sucking quietly on a nipple during the procedure.

Values for systolic and diastolic pressures were derived from 24 tracings in which no evidence of damping was present. Since mean arterial pressures are unaffected by damping, all 45 measurements were satisfactory for determining the range of mean pressures. The ranges for these pressures were as follows: systolic, 47 to 100 mm. Hg; diastolic, 26 to 62 mm. Hg, and mean arterial, 35 to 78 mm. Hg.

Although much variation is evident from these ranges, the readings tended to increase with increments in weight, surface area, postnatal age, and conceptional age (the sum of gestational and postnatal ages).

Serial blood pressure measurements for three infants having vascular or more advanced changes typical of retrolental fibroplasia were compared with similar observations on four infants with normal eyes. In each infant with eye abnormalities at least one measurement preceded the development of clinical fundus changes. Serial pressures in infants with retrolental fibroplasia were neither higher nor more suddenly elevated than those of the controls or of the group as a whole.

DISCUSSION

Dr. Richard L. Day, New York: I should like to ask Dr. Hepner what the final outcome was in the kitten eyes. Were any animals kept alive for observation of whether additional changes such as babies show would develop? Were the vessels in other parts of the body engorged? My co-workers and I have made some attempts, without success, to see whether the vessels in the other parts of the body of babies with retrolental fibroplasia are abnormal.

Were the changes in the vessels in the retina changes of proliferation or only of engorgement? If I interpret the statements of Owens, Blodi, and Reese correctly, the prime pathological lesion in the fundus is actually proliferation of endothelial cells.

DR. DANIEL C. DARROW, New Haven, Conn.: Judge Hand said to place a little confidence in simple explanations of complex phenomena. That is a queer remark with which to start discussion of work which I am inclined to believe is one of the best leads we have had on retrolental fibroplasia. Obviously, Dr. Laupus' explanation is going to be complex, but I think his lead is relatively simple.

I would think the changes were primarily dependent not on the blood vessels but on the peculiar type of cells in the retina. Dr. Yannet subjected cats to high concentrations of electrolyte in extracellular fluids. Unlike any other tissues in the body, the brain cells apparently become adjusted to the high osmotic pressure by releasing potassium from the cells, whereas in other cells apparently the adjustment is made by the shift of water, at least during short periods.

I would think Dr. Laupus' lead should be followed up not by production of edema but rather by looking for evidence of high concentrations of sodium in the serum and perhaps in some cases for evidence of brain damage as well as retinal damage. The lead is well worth following, and we are all grateful to him for giving us something else to do than to follow the false leads that have engaged our attention in the past.

DR. JOSEPH DANCIS, New York: I heard last week about Dr. Hepner's suspicions of transfusions and so took the opportunity to look through our own records to see whether we could cast further light on the problem. A group of us at Bellevue have kept rather careful records on retrolental fibroplasia for the past several years.

This slide demonstrates the incidence as graphed against time within our unit. (A slide was shown.) The heavy dark line is for the group under 3 lb. (1.3 kg.). As you can see, at this point we had a sudden dramatic increase in incidence. We were aware of no change in routine in the premature unit. We had been studying the question of vitamins, one of the false leads that Dr. Darrow commented upon, but we had made our change in use of vitamins nine months before this dramatic increase. We felt that that was negative evidence of some value, which tended to clear of suspicion the usual things done in the premature-infant unit. There had been no change in our formula. We were using olac throughout (incidentally, the sodium content of olac is 19.4 mEq. per liter), and we had made no change that I know of in our transfusion policy.

To check the question of transfusions more clearly, we compared the transfusion history of a group of infants with retrolental fibroplasia with that of a group of control infants who did not have this disease. We have had 28 cases of advanced retrolental fibroplasia, in which there was either retinal separation or scar; 29 controls were selected for comparison with the test group in birth weight within 250 gm. and in time of birth within six months.

The results were almost too good to be true. Sixteen infants in each group had received transfusions. The average volume of transfusion had been 17.3 cc. per kilogram in the test group and 17.7 cc. per kilogram in the control group. Of the 16 infants with retrolental fibroplasia who had received transfusions, 8 had had gross abnormalities in the fundi in the form of hemorrhages or retinal separation before transfusion. In our experience, when these advanced signs are seen, irreversible retrolental fibroplasia usually follows. Thus, in the control series retinal hemorrhages developed in only one infant and none had retinal separation.

A final point which may be significant, but which we cannot evaluate completely at present, is this: Dr. Guy, our ophthalmologist, has noted that retrolental fibroplasia develops only among infants who have shown some abnormalities during the first two weeks of life in the form of either vitreous haze or myopia. The opposite is not true—not all infants who show these findings acquire the disease. However, the statistical correlation between these early findings and retrolental fibroplasia is very high.

It would seem that we must still keep open minds as to whether the etiological factor in retrolental fibroplasia is operative antenatally or postnatally.

DR. JOSEPH STOKES JR., Philadelphia: I wanted to ask one very simple question. I believe those of you who have used corticotropin (ACTH)—Dr. Day and others—observed that although no improvement resulted no actual harm was noted. Since there is retention of sodium and often marked edema, I wonder how Dr. Hepner would explain this point.

DR STEWART H. CLIFFORD, Brookline, Mass.: We do not want Dr. Hepner to be discouraged by our apparent skepticism, but we have had so many leads that seemed equally promising but came to nothing.

I wonder whether he has any explanation for the early observation of these retinal changes, occasionally as early as in the first week after birth? I should like to point out that in our hospital, where retrolental fibroplasia was first recognized, it has been and still is the tradition to feed breast milk exclusively. It is true that about 50% of our premature infants go through Stage 3 and frequently Stage 4 and then have spontaneous regression.

We have also observed that when feedings are shifted from breast milk to cow's milk formula, with the same caloric intake, the babies spurt ahead in weight, and we assume that the weight gain is due to sodium retention. Perhaps it is important when an eye has reached Stage 4 to be careful not to add to the edema by making a shift to a mixture higher in sodium.

I should also be interested in knowing the outcome in the animals who showed changes, because we have been searching for a long time for an experimental animal in whom we could reproduce the disease.

I am grateful to Dr. Hepner for giving us another therapeutic tool. We all are acquainted with the extreme emotional tension that appears in the nursery when babies' eyes begin to develop through Stages 4 and 5. The demand that something be done is well nigh irresistable, making it difficult to establish a control series. The only treatment we have had to offer has been high oxygen therapy, and conceivably now we can offer one group of patients high oxygen therapy and the other a low sodium intake, thus setting up one group as the control for the other.

DR. ARILD E. HANSEN, Galveston, Texas: I want to take this opportunity to state that Dr. Hepner has paid strict attention in observing these babies' eyes. He has had an unusual opportunity, better than most of us have had, in that he spent about two years with an excellent ophthalmologist observing premature infants for every possible ophthalmologic detail. He knows the life cycle of this disease at least as well as any pediatrician. I think that his contribution has been the development of a new tool for study.

DR. HARRY H. GORDON, Baltimore: I agree with the comment made by Dr. Clifford, that regardless of the etiology of retrolental fibroplasia marked fluid retention might make it worse. I had an opportunity this morning to talk with Dr. Hepner and to hear more details of his method of feeding. I can confirm one of his findings, namely, that a sudden change in electrolyte content of the diet produces edema. Some 15 years ago, with such a change, we observed in two infants an actual bulging of the fontanel and a spread of the sagittal sutures. The infants showed no constitutional symptoms. No ophthalmoscopic examinations were made, but it is easy to believe that with expansion of cerebrospinal fluid space there might be edema of the retina and of the disks and engorgement of the vessels. And it may be that retinal attachment in premature babies is so tenuous that it will break under these conditions. Regardless, then, of the etiology of retrolental fibroplasia, overloading the circulation by large transfusions given too quickly or by sudden changes in electrolyte content of the diet may be harmful.

It seems worth calling attention to various errors in the care of prematurely born infants. One has to do with size of transfusions. The indications for transfusions in these infants are usually not cleancut. The physician is not ordinarily trying to treat shock or severe blood loss, and it would seem wiser to limit single transfusions to 10 ml. or less per kilogram of body weight rather than the customary 20 ml.

Another error has to do with the amount of salts ingested. Evaporated-milk mixtures without added carbohydrate have been recommended for feeding premature infants. The use of cow's milk to supply all the calories leads to an increase of 50% in the electrolytes above the level in the usual mixtures of evaporated milk and carbohydrate.

A great increase in electrolyte ingestion also occurs with improper use of concentrated feedings, those with 1 cal. per milliliter. These concentrated feedings are particularly suitable for infants who have defects in sucking and swallowing and who ordinarily gain satisfactorily with daily intakes of 90 to 120 cal. per kilogram. The feeding of 150 to 200 cal. per kilogram, and this in concentrated form, considerably increases total electrolytes to be excreted, with relatively less water than in more dilute feedings. One may then expect to find, as Dr. Darrow has mentioned, not only edema and expansion of blood volume, but also hyperelectrolytemia with noxious effects other than the one suggested by Dr. Hepner.

DR. L. EMMETT HOLT JR., New York: Dr. Hepner has made the point that a relatively transient trauma to the circulation, such as might be caused by an increase in electrolyte intake or by transfusions, has been responsible for the damage of retrolental fibroplasia. I should like to point out that a much more severe trauma to the circulation, namely the trauma of a birth, causes much more substantial damage and a considerable incidence of retinal hemorrhages. I want to know whether he or anyone else has correlated the development of retrolental fibroplasia with retinal hemorrhages following birth.

DR. W. R. HEPNER, Galveston, Texas: I should like to thank everyone for the generosity expressed.

Dr. Day wished to know the final outcome in the kittens' eyes. No eyes were observed long enough, nor were the conditions of the experiment carried out long enough, for us to discover whether a white retrolental mass would have been produced. All eyes were enucleated by the end of six weeks.

Dr. Day's second question was, were vessels elsewhere in the body engorged? I can answer that in terms of sections taken from the periorbital fat immediately behind the macular region in control and treated animals. These sections were taken because of the suggestion by Dr. Algernon Reese of the relationship between angiomata and retrolental fibroplasia. There was considerable periorbital vascular engorgement in the treated kittens as compared with the controls. Unfortunately, other organs or tissues of the body were not examined.

Dr. Day's third question was, were the retinal vascular changes engorgement or proliferation? I believe that both types were present in the kittens' eyes. It would be logical, I think, to say that engorgement of the major vessels would be necessary to supply the proliferated capillaries. I do not know whether or not it would be possible to state the corollary with the same degree of assurance. I cannot answer the question more fully.

The question as to whether variation in the course of the disease is due to treatment or to chance is very much to the point; this variation is one of the principal confusing factors in the study of retrolental fibroplasia. The reason we chose not to interfere with the natural course of the disease until retinal detachment or severe retinal edema with extensive hemorrhage in all four quadrants occurred was that a report on 72 infants from the New York Hospital showed that when these stages are reached reversibility occurs much less commonly than it does in the ealier stages of simple edema or simple engorgement with tortuosity and a few scattered hemorrhages. The "Retrolental Fibroplasia M&R Pediatric Research Conference Report" has a graph on page 30 which indicates that reversal of retinal detachment occurs in less than 25% of patients who have detachment under natural conditions.

Dr. Darrow asked, Were the changes primarily vascular or was there some peculiarity of the cells of the retina? I would be inclined to relate the vascular changes, if they are relatable, to the general body phenomenon, which can be seen as easily in the skin as in the eyes. Perhaps the reason this disease manifests itself principally in the eyes is that the eye in the more immature babies is in some way more peculiarly susceptible to damage. Some observers have stated that if a baby is born weighing 1,000 gm. he waits to get his disease until he weighs about 1,500 gm. But if a baby is born weighing about 1,500 gm., he may have his disease very soon, while he is regaining his birth weight and again approaching 1,500 gm. This observation is suggestive but of course proves nothing of a critical stage of development of the eye reached at about that point. The tremendous growth of the eye of the premature infant, who would normally be in the last trimester of intrauterine development, invites further investigation.

Dr. Darrow's suggestion of increased serum sodium levels is excellent and will be followed.

Brain damage related to retrolental fibroplasia is currently under investigation by Dr. Krause's group at the University of Chicago. Those of us who have studied this disease in terms of brain damage at that University, where we enlisted the aid of Dr. Douglas Buchanan for neurological evaluation, of psychologists who have devised all kinds of special tests for blind children, of psychiatrists who are helping us arrange situations so that the babies can grow up as normally as possible, and of all the social service supervision that is possible there, can say that only about 55% of the total of nearly 70 children are, at age 2 years, intellectually competent. By definition, competence in terms of the I. Q. means a functional level higher than approximately 60%. Others who have made similar studies are not in accord with this result. However, we find consistency in results with long-term clinical follow-up examinations.

Dr. Dancis raised the point again that there is marked fluctuation in this disease with no changes in treatment in the nursery at Bellevue. This is always a difficult kind of comment to answer. One wishes to ask, "Well, did you look for this, that, and the next thing?" You never know until you have looked. For instance, in Galveston our tap water is roughly 0.2 N saline, and if a formula of some powdered-milk preparation were made with tap water, obviously it would have an extremely high sodium content. Numerous other such remarks could be made, with no special profit.

As far as transfusion data are concerned, the principal application concerns what happens to the baby who has acute dilatation and tortuosity of his retinal blood vessels, with a little edema, when he is given intravenously 20 cc. of blood per kilogram of body weight. To discover the result, one must examine many infants immediately before transfusion and a few hours and perhaps a few days after to accumulate significant data. Our limited experience and the experience of others suggest that transfusion during acute retrolental fibroplasia worsens the disease.

Again, the individual susceptibility of each infant to this disease must be taken into consideration, since the feeling is growing that this disease is related to the degree of immaturity.

Dr. Stokes asked a question about corticotropin (ACTH). Originally corticotropin was thought to have real therapeutic usefulness. Broader experience with this drug, as with others, has reduced the original enthusiasm. So far as the dangers of corticotropin to premature infants are concerned, a number of workers have observed general sepsis with bacteremia after relatively short courses. This phenomenon would make me a little hesitant to use the drug unless I was sure it was going to be effective.

The question is, why should corticotropin work at all, according to the hypothesis forwarded in our papers, when it induces water retention and sodium retention? Corticotropin stimulates the adrenals of the premature infant, and the work of Robert Klein published in the *Journal of Clinical Investigation* some time ago indicated that infants who had retrolental fibroplasia and who were being treated with this drug had a marked water and sodium diuresis. Apparently stimulation of the adrenals of premature infants at certain stages of development produces an effect which is the opposite of the expected in terms of changes in sodium and water metabolism.

Perhaps this is why corticotropin sometimes works and sometimes does not—if given during the stage of development that allows diuresis it is effective, and if given later it is not. In effect, then, corticotropin may act as a diuretic, particularly and selectively for sodium and water. This explanation is based on other workers' evidence, not my own.

Dr. Clifford asked why there are sometimes early retinal changes, as within the first week of life. I cannot answer that question. I have not personally looked into enough eyes of such very small babies in the first week to be sure what is really going on. Most of the eyes I have looked into have been so cloudy that I was not able to see very much. I find vitreous hazing so common very early, particularly in tiny premature infants, that I suspect that it is "normal." When the vitreous clouding begins to clear, the retinal vessels are usually seen to be few, small in caliber, and short. As time passes, these vessels grow to approach a normal retinal vascular pattern. After this normal pattern has been established, the first vascular neoplasia begins if retrolental fibroplasia is to occur. Dr. Mary C. Fletcher has a significant volume of as yet unpublished data suggesting that this early vitreous clouding is merely a stage of growth and development of the very immature eye.

Dr. Clifford's next question is, how could retrolental fibroplasia develop in an infant on a human-milk diet? The difference is merely quantitative. Perhaps if there are many babies who cannot tolerate milk with 24 mEq. of sodium per liter, there are a few babies who cannot tolerate milk with 6.4 mEq. of sodium per liter.

I wish to thank Dr. Gordon sincerely for his comments, which were very helpful.

Dr. Patz asked from what part of the retina in the kittens the photomicrographs came. They came for the most part from the equator. Dr. Patz also asked where the signs of edema were in the kittens. They were general body signs, such as marked puffing of the eyelids, so that the eyes looked like those of frogs, and puffing of the paws, as though boxing gloves were being worn.

As to looking into the kittens' eyes to examine the retinae, we had extreme difficulty because of the vitreous clouding and because of the persistence of the embryonic vascular supply of the

lens in the kittens in which edema was severe and was maintained. This structure, incidentally, was maintained for as long as six weeks in two kittens by the manner described and after transfusion could be seen to have circulating blood. The retinal vessels were very large and were more crooked than those of the control animals.

Dr. Holt asks, why does not the tremendous transfusion which babies usually get at the time of birth, along with the common edematous state of the premature infant at the time of birth, do something to the eyes? He asks the question because these circumstances are the ones we incriminate later. We frequently do see retinal hemorrhages in premature and full-term babies alike in the immediate neonatal period, but we do not see retrolental fibroplasia then. Apparently the placenta in some way protects the infant in utero from developing the primary vascular lesions of early acute retrolental fibroplasia, so that the transfusion received at birth is innocuous and cannot contribute to the development of the disease as it does in the infant lacking "placental protection" against the other factors which bring on the original vascular neoplasia of acute retrolental fibroplasia. Except for this speculative explanation, I cannot answer the question.

Observations on Body-Water Concentration Homeostasis of Children with the Nephrotic Syndrome. Dr. John D. Crawford, Dr. Charles D. Cook, and Dr. Barbara Pinkham, Boston.

The data presented describe functional aspects of the water metabolism of a group of children with the nephrotic syndrome. These patients have in addition to an abnormally large body-water content a significant increase in the water concentration of plasma and extracellular fluid roughly proportional to the degree of edema. When subjected to water restriction they have a prompt and effective antidiuretic response which serves to maintain essential constancy of the abnormally high water concentration of the extracellular fluid. Conversely, when loads of water are administered, constancy of the water concentration in plasma is assured by a diuretic response quantitatively comparable to that observed in similarly loaded normal subjects. Occasional failures to respond by diuresis to orally administered water loads may be due to failure of gastrointestinal absorption of the water. This hypothesis is suggested by dilution studies after oral loading and by the prompt excretion of an intravenously administered load. The diuretic response can be inhibited by administration of small amounts of vasopressin injection (pitressin®) or by stimulation of endogenous production of antidiuretic hormone by epinephrine administration.

The data show that on the group of nephrotic children studied the abnormal status with respect to body-water content and extracellular-water concentration is not a result of a limitation in renal capacity for water excretion and is not due to a pathologic overproduction of antidiuretic hormone. Rather, they suggest that these nephrotics' water metabolism is regulated in a manner comparable to that of the normal person but at a level which is quite different. Interpretations of these phenomena were offered.

DISCUSSION

Dr. Harold E. Harrison, Baltimore: Dr. Crawford has reversed the usual terminology by expressing his data in terms of water concentration rather than in terms of solute concentration. Of course in essence what he means is that the patients have a lower concentration of solutes per liter of water in the serum, and of course most people are accustomed to thinking in terms of the concentration of sodium per liter of serum water.

I should like to point out that the homeostatic regulation of water concentration is disturbed in disease in which there is no edema or sodium accumulation. A striking example is tuberculous meningitis. In this disease the water homeostasis, to use Dr. Crawford's term, is so altered that most children with the disease have a very high concentration of water per milliosmole.

Giving sodium to these patients does not restore the normal serum water. They tend to maintain their abnormal serum-water concentration until their tuberculous meningitis is in a state of remission as a result of therapy.

We have found that in some of these patients there has been a striking reduction in the concentration of potassium in the muscle cell, as well as alterations in the sodium content of the red cell. If one tries to correlate all these studies, one is likely to find that primary changes in cellular composition are always responsible for disturbances of osmotic concentration of extracellular water.

DR. GLADYS J. FASHENA, Dallas, Texas: My group has been interested in this problem for several years and has carried out water-loading experiments in a somewhat different manner. We now have observations on some 35 normal persons and approximately 16 edematous nephrotic patients. The water loading was done by the oral route, 5% of the body weight being given at the rate of 1% an hour, and then the water excretion was observed for approximately 12 hours. We have also carried out independent studies of sodium loading which are not pertinent to the present discussion.

Although there is some variability in our results from one patient to the next, most of our edematous nephrotic patients have shown a marked disturbance in water excretion. The two most striking findings are that the velocity quotients (Adolph) for the excretion of water are generally much lower than normal and that as a consequence the cumulative load in any given hour becomes much greater than it does in the normal person. It is true that nephrotic patients eventually excrete the load, but it often takes them a couple of days to do this, whereas the average normal person will have excreted his load in 8 to 10 hours.

We attempted to find out whether or not this phenomenon might be attributable to the fact that in the edematous patient, whose extracellular volume is greatly expanded, the water load might possibly not dilute the body fluids to the same degree as in the normal person and therefore the osmoreceptors might not have the opportunity to respond in a normal manner. We tried to solve the problem by determining plasma specific gravity by means of the Linderstrøm-Lang gradient tube. We were able to demonstrate appreciable dilution of the plasma after loading both in normal and in nephrotic persons, and so this does not appear to be the explanation. Incidentally, the finding of a lowered specific gravity would indicate that an appreciable amount of the administered water had been absorbed from the gastrointestinal tract.

We extended our observations to other types of edematous patients, namely, those with hepatic and cardiac edema. The same general findings were noted. In fact, we have wondered whether the dysfunction in water excretion was related to the presence of edema rather than specifically to the nephrotic syndrome. We also have some observations on nephrotic patients before and after diuresis, both spontaneous and corticotropin-induced. In every instance after the diuresis the nephrotic child responded to a water load like a normal child.

DR. JACK METCOFF, Boston: Dr. Crawford has done a beautiful job in presenting an interesting concept. Some 30 years ago, Dr. L. W. Hill was interested in the problem of the renal loss of water after the drinking of large quantities of water in the presence of renal disease with edema and demonstrated essentially the same pattern of response which Dr. Crawford and associates have so beautifully and specifically shown.

The concept which Dr. Crawford presents is consistent with that of other investigators who have found either a qualitative variation in response or a slight quantitative variation in excretion of electrolytes or of water. The data of Crawford and associates provide, further, specific evidence that limitation of excretion of salt and water may not be a fundamental feature of the nephrotic syndrome.

There are two points I should like to have clarified. I noticed on the charts the very large apparent insensible loss of water in the nephrotic syndrome. This loss in a period of 175 minutes on one of the charts amounted to, I believe, something like 30 to 40% of the administered water load. This strikes me as an amazingly large figure for insensible loss, particulary in this disease. Second, I wonder whether the actual content of water per kilogram of serum has varied in the nephrotic patient from time to time. As far as my group has been able to tell by direct measurement in the presence of varying degrees of edema, the actual quantity of water present per kilogram of serum is not remarkably disturbed.

DR. JOHN D. CRAWFORD, Boston: I want to thank Dr. Harrison for bringing to mind another condition in which one would presume there is a high serum water concentration but no edema.

I am very much interested in Dr. Fashena's observation that in nephrotics, in whom there is a delay in the excretion of a water load, she finds specific gravity changes in the blood equal to those in the normal person similarly loaded. That observation is contrary to our experience with the freezing point method for estimating changes in serum water concentration.

Dr. Metcoff asks about the large figures for insensible water loss shown on the slides. In drawing the vectors for extrarenal and minimal renal water losses, we had to take the liberty of averaging results in order to get five or six curves on the same slide. Nevertheless, the average is representative of our experience in the children's metabolic unit. We find insensible water losses that are quite large as compared with those reported in the literature. We believe that the explanation for this discrepancy lies in the fact that our measurements have been made over 24-hour periods on patients allowed as much activity as they wished. Most of the figures in the literature have been extrapolated to 24 hours from measurements over short periods on patients at so-called basal levels of activity.

We have made only a few gravimetric measurements of the serum water content of nephrotic patients. A priori, one would not expect a direct correlation between water concentration per mass unit of serum solid and water concentration per osmotic unit of serum solute. Under certain circumstances, however, a rough parallelism may be found.

Mucolytic Enzyme Systems: XVIII. Nonspecific Hyaluronidase-Inhibitor Concentrations in the Blood Serum of Siblings and Parents of Children with Rheumatic Fever.—Dr. Forrest H. Adams, David Glick, Ph.D., Dr. Ray C. Anderson, and Dr. Paul Dwan, Minneapolis.

Genetic susceptibility of the host to rheumatic fever appears to be an important factor in the acquisition of this disease. An intriguing possibility exists that there is, at least in part, a biochemical basis for the difference between rheumatically susceptible and nonsusceptible persons. It has been shown that rheumatic fever patients appear to respond to streptococcal infections with a greater production of antibodies to the streptococcal antigens. These observations of the antibody response, however, have not been extended to other members of the family.

In earlier communications Good and Glick and Dorfman described an elevation of the serum nonspecific hyaluronidase inhibitor in the early phases of rheumatic fever with subnormal inhibitor levels occurring in the period of convalescence from this disease. It was the experience of Good and Glick and also of ourselves that patients with convalescent and inactive rheumatic fever regularly had subnormal serum hyaluronidase-inhibitor values. Good and Glick were unable to decide whether the consistently lower values noted had a special significance, but they stated: "It is certain from extensive clinical studies that patients such as those studied in this group represent a population more susceptible to the ravages of rheumatic disease than groups of normal children. If hyaluronidase activity plays a role in the pathogenesis of rheumatic fever, the differences in serum inhibitor concentrations might have considerable bearing on the relative susceptibility of various individuals to rheumatic disease."

No studies have been performed to date to demonstrate whether persons in whom rheumatic disease develops have low hyaluronidase-inhibitor levels before the onset of the disease. The possibility exists, however, that such levels might occur. If susceptibility to rheumatic fever is in part due to genetic factors and susceptible persons have low hyaluronidase-inhibitor values, these low values might also be found in the sera from a significant percentage of siblings and parents of the rheumatic fever subjects.

The purpose of this communication is to report the results of studies on the concentration of the nonspecific hyaluronidase inhibitor in the sera of 64 parents and 67 siblings of rheumatic fever subjects and to compare the data with those from 71 normal persons from families in which no known cases of rheumatic disease had occurred.

The viscosimetric method previously employed was used for the determination of the nonspecific hyaluronidase inhibitor in the blood serum. The concentration of the inhibitor was expressed in terms of percentage inhibition of the activity of a standard bovine testicular hyaluronidase preparation acting on a standardized hyaluronic-acid substrate prepared from human umbilical cords.

Forty-three parents and siblings (33%) had values below 15% inhibition of hyaluronidase, whereas only seven normal persons (10%) had such low values. This difference was found to be statistically significant.

DISCUSSION

Dr. Herbert A. Wenner, Kansas City, Kan.: To disregard the aspects of genetic susceptibility for the moment, it has been shown by a number of observers that there is a specific

inhibitor for Group A hemolytic streptoccoci hyaluronidase which appears and increases in titer during streptococcal infection. Patients with rheumatic fever in particular have a high anti-hyaluronidase titer.

With these few remarks I should like to make another comment, I believe some of the nonspecific-inhibitor studies could well be correlated with studies on specific-inhibitor titer, and I should like to ask two questions: First, have Dr. Adams and his co-workers attempted to compare titers of specific and nonspecific inhibitors? Second, is a nonspecific inhibitor related to any serum protein fraction or is it always, as it is in some cases, a mucoprotein or a lipoprotein?

DR. MAY G. WILSON, New York: I think Dr. Adams is to be congratulated on his approach and that his work should stimulate other studies. When the nature of the inherent defect responsible for susceptibility to rheumatic fever is known we may understand more about this obscure disease.

One precaution must be taken, however. In heredity studies one must be certain of the incidence of susceptible persons. Among the parents and siblings in his group, as Dr. Adams is probably aware, there were some nonsusceptible persons. The differences he observed may have been due to the presence of nonsusceptible members in the so-called susceptible families. The only families which can be considered to have 100% susceptible members are those in which both the mother and the father are rheumatic.

Also, one would have to consider that the normal group may have included some susceptible persons. A susceptible person cannot be identified unless both parents are rheumatic. If both parents are rheumatic, it can be assumed that all children are susceptible.

We approached this problem several years ago, using the method of Dorfman. We found no difference in the range of hyaluronidase titers among susceptible persons, proved susceptible persons (i. e., rheumatics), and nonsusceptible pedigreed families. When we compared the titers in children regardless of whether they are actively rheumatic, inactively rheumatic, susceptible, or normal, we observed no differences when these groups were correlated with respect to antecedent infection.

DR. A. E. HANSEN, Galveston, Texas: I want to ask Dr. Adams whether the levels in patients who had streptococcal infection, ordinary infection, dropped abnormally low.

DR. FORREST H. ADAMS, Minneapolis: We have made no studies in which we have followed both the nonspecific hyaluronidase inhibitor and the specific hyaluronidase inhibitor, but we have contemplated such studies. As you will recall, the nonspecific hyaluronidase inhibitor is not antibody. It is a protein substance that has been fairly well characterized by Dr. David Glick, who is one of the authors of this paper. Dr. Glick believes that the nonspecific inhibitor is a heparin-like substance.

In regard to the question whether patients with infectious disease, particularly streptococcal disease, have such low inhibitor values after the acute infection, this problem has been studied by Dr. Robert Good, of our department, and he has found that such persons have a return to normal values rather than to the subnormal values observed in the case of rheumatic fever patients.

In regard to Dr. Weech's comment, perhaps I did not make myself clear. It was stated in the introduction of our paper that the siblings and parents who were tested had not had rheumatic fever as far as we were able to determine. We did not examine all these siblings and parents, but they said that they had not had rheumatic fever.

Also in answer to Dr. Weech, the 15% hyaluronidase inhibitor was chosen as a dividing line because the statisticians had advised us that in order to use the fourfold table method there should be at least five individuals in each one of the four groups.

Experimental Feeding Tests with Lactobacillus Acidophilus. DR. EDWARD L. ROBINSON, and WALTER L. THOMPSON, PH.D., Hamilton, Ohio.

Although it has been known for many years that breast-fed infants thrive better during the first few months of life than do infants fed cows' milk formulas of the same protein, fat, and carbohydrate level, the reasons are still uncertain.

One of the most striking differences between the two groups is the bacterial content of the intestinal tract and stool. The stool of the breast-fed infant is distinctly acid, and the pre-

dominating organisms are Gram-positive lactobacilli, whereas in the case of the artificially fed infant the stool is much less acid and the Gram-negative coliform-aerogenes group predominates. In addition, recent work has shown that synthesis by the intestinal flora can be a significant source of vitamins and other essential growth factors.

An exploratory experiment on the possible nutritional significance of the two types of flora was undertaken.

Approximately 800 infants born at the two cooperating hospitals over a six-month period were fed their prescribed formula, supplemented daily during their hospital stay with 500,000,000 viable Lactobacillus acidophilus cells and/or 2 mg. of folic acid per quart of formula, and their gains in weight measured at the end of one month.

Stool smears for a selected group of infants after four to five days showed implantation of Gram-positive rods in the intestinal tract of those fed L. acidophilus, while a Gram-negative flora predominated in the controls and those fed folic acid. Additional smears for this group at one month showed that the Gram-positive flora persisted in the infants receiving the culture supplement provided they remained on a predominantly milk diet.

It was found very early in the work that babies who were nursed, even for only one or two days, showed a remarkable gain over those who were completely bottle-fed, particularly in the control group. After this observation had been made, the infants were further divided into two subgroups: infants partially breast-fed, and those completely bottle-fed.

On the basis of the experimental results it was concluded that:

1. Infants partially nursed, even for two or three days, showed significantly greater gains in weight during the first month than did infants completely bottle-fed.

2. Bottle-fed infants on formulas supplemented with L. acidophilus showed significantly larger gains in weight during the first month than did the controls. The gains in weight approached, but did not quite equal, the gains of partially nursed infants.

3. The addition of 2 mg. of folic acid per quart of formula had no significant effect on the gain in weight of either bottle-fed or partially breast-fed infants.

4. The addition of L. acidophilus to the formula had no effect on the gain in weight of partially breast-fed infants.

5. There appears to be no unknown factor or factors present in colostrum which causes increased gain in weight during the first month of life. A considerable part of this increase can be obtained by supplementing the formula of the completely bottle-fed infant with L. acidophilus for the first few days of life.

DISCUSSION

DR. A. ASHLEY WEECH, Cincinnati: I think the statistics are fine, but I should like to know whether the culture was incubated in the milk for some time before it was fed or just dumped in prior to feeding.

DR. WALDO E. NELSON, Philadelphia: I do not intend to discuss the contents of the paper. What the ultimate significance or importance of the data presented will be I do not know.

The comment I should like to make is based on a rapid survey of this year's program. I do not note any other papers by persons who are not attached to a medical school or to a non-university large medical center. It has long seemed to me that there is a real need for participation in clinical investigation by physicians in private practice. For this reason I should like to compliment a man who during a busy practice found the stimulus and energy to plan and carry out the clinical study which has just been presented.

THIRD SESSION

WEDNESDAY, MAY 7

Hemorrhagic Disease in an Infant Due to Deficiency of a Previously Undescribed Coagulation Factor. DR. IRVING SCHULMAN and DR. CARL H. SMITH, New York.

Recent studies in the field of coagulation have extended greatly the knowledge of this vital function. These contributions, together with new methods and techniques, have led to clarification and precise definition of various hemorrhagic syndromes previously classified into ill-

defined groups such as "pseudohemophilia," "parahemophilia," and "hemophilia-like disease." The present investigation appears to demonstrate the existence of a previously undescribed factor necessary for normal coagulation and a hemorrhagic disease due to its lack.

The patient upon whom these studies were performed was an 11-month-old boy who was brought to the hospital with an acute onset of transverse myelitis which was found, on surgical exploration, to be due to a large hematomyelia of the cervical spinal cord. The family history was entirely negative for hemorrhagic disease, but routine coagulation studies on the patient demonstrated findings typical of hemophilia, namely: markedly prolonged clotting and recalcification times; abnormal prothrombin consumption; normal bleeding time, platelet count, and clot retraction time, and normal calcium, fibrinogen, and prothrombin concentrations. Further investigation, however, demonstrated that the patient's coagulation defect was quite different from that in hemophilia. His whole blood and plasma corrected completely the abnormal clotting time of all hemophilic bloods tested. Similarly, hemophilic blood or plasma corrected completely the coagulation abnormality in the patient. In addition, the patient's blood or plasma corrected the defective prothrombin consumption in hemophilia, and vice versa. These data indicated that the factor deficient in hemophilia was supplied by the patient's blood and that the factor deficient in the patient was supplied by hemophilic blood.

Circulating anticoagulants as well as abnormal amounts of antagonists to all known coagulation factors were ruled out. Plasma and serum accelerator globulins were found to be present in normal concentration. By means of silicone technique the role of the platelets was investigated and the platelet activity found to be normal. Plasma fractionation was carried out in an attempt to localize the deficient factor, and in normal plasmas it was found to exist in the same fraction as the antihemophilic globulin. Fractionation of hemophilic plasma, however, yielded a fraction which corrected the patient's coagulation disorder but was ineffective in hemophilia. The deficient factor was thus found to be a plasma protein but one distinct and separable from the antihemophilic globulin.

Further study indicated that the deficient factor was involved in the formation of active thromboplastin, and three possible modes of action were suggested: (1) the factor was a thromboplastin precursor in addition to an antihemophilic globulin; (2) the factor acted as an enzyme in the reaction of antihemophilic globulin and platelet factor; (3) the factor acted as an activator of preformed thromboplastin.

These findings, in a child whose routine coagulation studies so closely simulated those in hemophilia, suggested that this syndrome might explain certain cases of sporadic hemophilia. Thus far four patients with sporadic hemophilia have been tested. Their blood, however, reacted as did that of the usual patient with familial hemophilia and was distinguishable from that of the patient. Nevertheless, it appears likely that further study will disclose other cases of the type described.

DISCUSSION

DR. CARL H. SMITH, New York: I believe it would be of some value to review briefly the circumstances under which the absence of this new coagulation factor was discovered. The existence of the defect in this child was demonstrated indirectly by eliminating successively the established coagulation factors. The eventual isolation of this newly discovered factor will, of course, depend ultimately upon its fractionation from plasma. This defect in coagulation may not be peculiar to this child but may be present in other cases of sporadic hemophilia. The practice heretofore has been to classify as having hemophilia every male patient with uncontrollable bleeding who shows evidence of markedly prolonged clotting time. The recognition of an undescribed deficiency in the present case justifies the reexamination of other patients with hemophilia with bizarre clinical features.

The train of events in this case differed from that in the usual case in that the onset was at 11 months of age and was marked by a convulsion. There were no noteworthy hemorrhagic manifestations in the previous history. The sole suspicion of a blood dyscrasia early in the course of the present illness was an excessively low hemoglobin content. Severe hemorrhage occurred only as a complication of the operative procedure, when appropriate investigations for a bleeding diathesis were undertaken. The laboratory observation of a prolonged coagulation time was not made until some time after the termination of transfusion therapy. The important clue that this patient differed from a true hemophiliac was that his blood restored the clotting

time of a known hemophiliac to normal and that the reverse also took place. This observation led to the series of studies presented and should serve as a convenient screening test in suspected cases.

An initial step in blood coagulation depends on the activation of plasma thromboplastinogen by a platelet factor. By definition the defect in hemophilia is related to a congenital deficiency of thromboplastinogen. However, the addition of our patient's blood to that of a hemophiliac led to the restoration of normal clotting. The hemophiliac could not supply thromboplastinogen to the patient, nor could the reverse occur if he was a hemophiliac. With a normal prothrombin content, the presence of accelerator factor, the absence of a circulatory anticoagulant, and elimination of the platelet as the responsible element, it seemed plausible that the clotting defect could be attributed to the absence from the plasma of a previously undescribed coagulation factor.

The absence of this essential factor in coagulation is comparable to another plasma defect described in a paper in an earlier session—namely the absence of gamma globulin. In summary I should like to emphasize the importance of scrutinizing cases of sporadic hemophilia in the manner outlined by Dr. Schulman. It is barely possible that further experience may reveal the existence of this defect on a familial basis. For the present the treatment in this case differs in no respect from that of the conventional hemophiliac.

Total Body Exchangeable and Erythrocyte Potassium Measurements in Children with the Nephrotic Syndrome. Dr. Donald Gribetz, Dr. Leslie Corsa, Dr. Charles D. Cook, Dr. Hans Keitel, and Helen Berman, Boston.

In the course of a series of investigations concerning the physiological adjustments which take place during the nephrotic syndrome, studies of the body potassium content were performed, two in vivo techniques being utilized: (*a*) measurement of the exchangeable potassium by the isotope-dilution principle and (*b*) determination of the potassium content of the red blood cell.

For the purposes of comparison, studies of the exchangeable potassium were determined on 13 "hospital normal" children and efforts were made to find the appropriate common denominator with which to express the values. Observations were made on nine nephrotic children, all of whom showed the typical clinical, blood, and urinary findings of the syndrome. The values for exchangeable potassium obtained from nine determinations on seven of these children were correlated with weight, height, and urinary creatinine, as were the data from the normal children.

When plotted against weight, the exchangeable potassium demonstrated an approximately straight-line relationship for normal persons (the data include values for adults obtained from the literature in addition to the data for normal children). As was to be expected, the exchangeable-potassium data for nephrotic children were low when related to edematous weight. When corrected for an observed nonedematous weight, however, the values with one exception moved into the normal range, a range of 32 to 47 mEq. per kilogram with a mean of 40 mEq. per kilogram.

When correlated with height in an effort to remove the factor of edematous weight, the exchangeable potassium again showed a definite relationship, but this time an asymptotic-like correlation. With two exceptions, the nephrotic values again fell within the normal range. These exceptions may have been due to muscle wasting coincident with chronic disease.

A correlation was therefore constructed between urinary preformed creatinine and exchangeable potassium, since both these substances are derived chiefly from the body's protoplasmic mass. Here a definite straight-line relationship was described by the normal data. When compared, five values obtained for four nephrotic patients demonstrated precisely the same relationship.

In conjunction with the isotopic measurements, 15 red blood cell potassium determinations on eight of these children were performed. In all save two the values were within the normal range, a range of 87 to 97 mEq. per kilogram of red blood cells.

Two general conclusions can be drawn: (1) the body potassium content as determined by the exchangeable-potassium method, although correlating well with weight and height, appears in the normal person to show the best relationship to urinary creatinine; (2) the data from nephrotic children when compared with these relationships failed to demonstrate any significant deviations from the normal.

The gross changes of water and sodium metabolism which occur in the nephrotic appear, therefore, to be unaccompanied by similar large changes in potassium. This observation was corroborated by balance studies performed on three of the children which showed no marked potassium gains or losses. Although minor deviations in potassium content cannot be ruled out because of the inherent error of the methods employed, gross deviations apparently do not occur.

DISCUSSION

DR. WILLIAM M. WALLACE, Boston: We heard yesterday that the concentration of water in the body in nephrosis is high. In the language of the man in the street, as Dr. Harrison pointed out, that means that the osmolar concentration in the plasma of nephrotic patients is low.

Today we have heard that the concentration of intracellular electrolyte is normal. It seems to me we have now heard the statement made that the two phases are out of osmotic equilibrium.

There is a normal concentration of base in the intracellular and a subnormal concentration in the extracellular fluid. I think we have all been brought up on the concept of osmotic equality between the body fluids. I wonder whether we must now throw that out.

I should like to draw the authors of this paper and of the one we heard yesterday out on that question a little bit.

DR. GEORGE M. GUEST, Cincinnati: The thesis that changes in electrolyte composition of erythrocytes may serve as an index of similar changes occurring concomitantly in other soft tissues of the body is one that I have pursued many years; thus I am especially interested in the excellent studies done by Dr. Gribetz to advance such a thesis.

It seems pertinent to mention here certain studies done in our laboratory on organic acid-soluble phosphates of the blood cells in relation to cellular potassium. Several groups of investigators have supplied evidence that the transfer of potassium into and out of red blood cells is accomplished by enzyme systems involved in glycolysis and in the metabolism of the phosphoric esters of the cells. This is an extremely labile system, in which processes of breakdown and resynthesis of the organic phosphates are continuous but in equilibrium as long as the concentration of the organic phosphates is maintained constant. In certain pathologic conditions decreases and increases in concentration of the organic acid-soluble phosphorus in blood cells are closely associated with parallel changes in concentration of cellular potassium; for example, both values decrease in diabetic acidosis and rise together during recovery, In nephritis with retention, i. e., with elevated nonprotein nitrogen and inorganic phosphorus in the blood plasma, the concentration of organic acid-soluble phosphates in the blood cells may be tremendously increased.

In a series of cases of the nephrotic syndrome in children with normal renal function studied in our laboratory some 15 years ago (unpublished), we found few if any abnormal values for the concentration of organic acid-soluble phosphorus in the blood cells. Recalling those studies, I would expect the values for cellular potassium also to be within normal limits in nephrosis, as reported by Dr. Gribetz.

DR. DANIEL C. DARROW, New Haven, Conn.: I am not sure that this paper calls for much comment. The data and conclusions seem well within the accuracy of the methods.

I do not believe Dr. Wallace is correct when he implies that the authors regard their data as proving a difference in the osmotic pressures of intracellular and extracellular fluids. I do not recall any mention of total body water, and therefore their data cannot be used to discuss concentrations in water. Furthermore, distribution of body water was not brought up, so changes in concentration in cellular water cannot be discussed.

However, since Dr. Wallace brought up the question, he at least invited us to discuss the evidence for osmotic equilibrium between extracellular and intracellular fluids. The postulation of osmotic equality may be supported in quite simple terms. Since the cell membranes are not rigid structures, their shape is determined by pressures inside and outside the cells. If the osmotic pressure were high in the cells, their shape would be round and not determined by the small pressures of surrounding structures. Other simple observations, such as those reported by Yannet and me, leave little doubt in my mind that the osmotic pressures of most parts of body water are practically the same.

The data reported by Gribetz bring out nicely that body potassium is related to cell mass. I was surprised that potassium was so precisely related to creatinine excretion.

I should like to call attention to the fact that the data supported the relation of potassium to fat-free solids. McCance and associates have given us nice data which show that the composition of fat-free solids is relatively constant. They report the conclusions which this assumption leads to in subjects with edema and varying degrees of adiposity.

From their studies they conclude that body composition can be considered to consist of (1) extracellular water and electrolytes; (2) intracellular water, solids, and electrolytes, and (3) fat. It follows that body composition can be calculated from a determination of total body water and extracellular water. Total water minus extracellular water gives intracellular water, which is normally associated with constant solids and electrolyte per unit of water.

Unfortunately, the determination of body potassium by isotope dilution is somewhat less than total body potassium. However, we are on the threshold of being able to determine approximately the composition of the body in living subjects. Isotope dilution should be used in connection with McCance's assumptions to estimate the reasonableness of the conclusions with respect to body composition.

Dr. Carleton Gajdusek, Washington, D. C.: Dr. Darrow has pointed out that the isotope-dilution techniques for determining the total or exchangeable body concentration of any element are subject to certain errors. In view of the paper yesterday in which measurement of total body water was based on a deuterium determination, we naturally may bring to mind the possibility that a relatively large amount of water may be protein-bound. Therefore we are uncertain, a priori, just how much equilibration will take place between the protein-bound water and the other water of the body that is more easily equilibrated. I ask for information on control studies in which the extent of exchange of water intimately bound to the structural proteins of the body has been estimated for the period of equilibration employed.

Similarly, with regard to any isotope determinations using potassium, I am not aware that the authors told us exactly what the relation is between total body potassium and exchangeable potassium. They have wisely followed Dr. Corsa's suggestion and used the term "exchangeable." I wonder whether they have used small laboratory animals to settle the relation between "total" and "exchangeable" potassium.

It would be relatively simple to use a similar technique with the same period of equilibration to determine exchangeable potassium and then to kill the animals for accurate gravimetric determination of total body potassium. I realize the danger of extending the conclusions from animal work of this sort to the human. Here the danger should be small. Many papers in which these isotope techniques are described leave us wondering how close to the total body content of an element the dilution technique brings us within the period of equilibrium allowed. The authors have not told us of their control animal experiments.

Dr. Jack Metcoff, Boston: I wonder whether the authors would care to speculate as to how their data relate to the tissue analyses in nephrotic patients done by Fox and by Mudge. Both demonstrated a low intracellular potassium content in muscle.

Dr. H. G. Keitel, Boston: Dr. Wallace has inquired about the mechanisms which sustain osmotic equilibrium between cells and plasma in nephrosis, and Dr. Darrow has stated that our data were insufficient to form the basis for a discussion of this point. The red cell data presented by Dr. Gribetz were limited to the red cell potassium content, no mention having been made of the osmotic relations with plasma.

Unreported observations on these patients show that their red cells contain a normal amount of water as well as of potassium, but a slightly less than average amount of sodium. As far as the plasma is concerned, there is an elevated water, a reduced sodium, and a normal potassium content per kilogram. While both red cells and plasma have a reduced sodium plus potassium concentration in water as compared with normal persons, the reduction is more pronounced in the plasma.

These data cannot be interpreted as indicating the absence of osmotic equilibrium between red cells and plasma in nephrosis, for only a portion of the potential osmoles were studied. It is not known whether these differences are accompanied by corresponding differences in total osmotic pressure.

Dr. Donald Gribetz, Boston: I should first like to thank the discussers for their kind remarks.

I believe Dr. Corsa's original paper on the exchangeable-potassium method (*J. Clin. Invest.* **29**:1280, 1950) covers the point raised by Dr. Gadjusek. Dr. Corsa has done exactly what has been suggested, using the rabbit. He found that when a 40-hour equilibration period is utilized for the exchangeable-potassium method, the results are within 5% when compared with total body potassium values obtained by chemical analysis of the carcass. Since we are using a shorter equilibration period for our studies, namely 24 hours, we have estimated that 10% of the body's potassium is not being measured.

Dr. Metcoff has commented on the discrepancy between our findings and those of Fox and Slobody (*J. Pediat.* **7**:186, 1951). Although this was not the main purpose of our studies, it is evident that by means of the in vivo techniques used we have been unable to confirm the low potassium values which they found in postmortem samples of muscle obtained from children with the "nephrotic syndrome." There are several factors which may shed some light on these discrepancies: (*a*) the patients studied by Dr. Fox were apparently in different stages of the nephrotic syndrome, that is, they had advanced chronic nephritis; (*b*) they had all received alkali therapy in the form of potassium acetate and sodium lactate, and (*c*) the studies were performed on postmortem tissue.

Dr. Guest asked if we have found any correlation between body potassium content and transient changes in pH, nonprotein nitrogen, and serum phosphorus. We measured these variables and found no systematic relationship to body potassium. Serial measurements, however, were not performed, and therefore we cannot draw any definite conclusions on this point.

I think Dr. Keitel has attempted to answer Dr. Darrow's comments, and in relation to his and Dr. Wallace's statements, we should like to say that that the data are being presented chiefly for their descriptive value. Their significance with regard to questions of cellular osmotic status remains to be determined.

Mucoviscidosis with Partial Pancreatic Insufficiency. Dr. Harry Shwachman, Dr. H. Leubner (by invitation), Dr. P. Patterson, and Dr. C. C. Weill (by invitation), Boston.

Our present concept of mucoviscidosis is that of a generalized disease. The clinical manifestations may be predominantly related to the pulmonary involvement, with relatively little evidence of pancreatic disturbance. In the past a number of cases were undiagnosed because the conventional examination of the duodenal fluid for trypsin usually gave normal results. Partial pancreatic insufficiency has been demonstrated in some cases. The observations that a loss of pancreatic enzyme activity can occur in serial examinations in the same patient and that there may be a dissociation of the activity of the various enzymes usually found in duodenal fluid were discussed.

Partial pancreatic insufficiency can be demonstrated by a number of techniques, some of which are new and presented here for the first time. In our study of duodenal fluid, viscosity and pH were measured. Proteolytic activity was determined by using a variety of substrates and measuring a corresponding number of enzymes. This procedure includes the determination of carboxypeptidase, which splits a specific type of peptide bond.

Simultaneous determinations were made of other enzymes, notably amylose, lipase, and esterase. The acid and alkaline phosphatases were also measured. These enzymes were measured before and after stimulation of the pancreas with olive oil. The nature of the response reflects pancreatic function.

Serial duodenal-fluid assays or repeat observations on the same patient suspected of having this disease (especially siblings of patients) showed that we may be dealing with a progressive disease. Partial insufficiency exists in the early stages in such patients.

In addition, partial deficiencies involving defects in proteolytic activity can be measured indirectly by feeding proteins orally and measuring the response of the plasma aminoacetic acid. A number of illustrative cases were included.

DISCUSSION

Dr. Douglas E. Johnstone, Rochester, N. Y.: Although I do not agree entirely with some of the conclusions drawn by Dr. Shwachman, I think he is to be commended for this work because there is a great need further to differentiate some of the entities that have in the

past been grouped under the celiac syndrome. The status is much the same as that of congenital heart disease many years ago. The need for defining the various entities is important, because with the present interest in cystic fibrosis, the condition of some children is being falsely labeled as that, and this diagnosis creates a great deal of psychological trauma in the families.

I should like to ask Dr. Shwachman a few questions. In regard to the serial examinations for trypsin, was it always certain that the proteolytic action was due to trypsin and not to bacterial gelatinase?

I think one can honestly differentiate between some proteolytic enzymes only through specific-inhibitor systems or by immunizing, say, a rabbit with one of the enzymes and making a specific antibody against it, let us say differentiating between proteolytic activity due to trypsin and that due to carboxypeptidase.

With regard to viscosity, I should like to ask Dr. Shwachman whether he feels that gastric mucin might influence the viscosity of duodenal juice, irrespective of the state of viscosity of the pancreatic juice. I also want to ask him whether he feels that olive oil is as good a stimulus for pancreatic juice as secretin. Olive oil, as is known, will drastically influence the gastric emptying time of the patients, will usually promote rapid emptying of the duodenum, and may actually alter the quantities of enzyme. It may stimulate the bile. With secretin, one is perhaps more likely to get an increased flow of duodenal juice, which, among other things, may give a better chance for estimation of the true free-alkali output by the pancreas.

I should also like to ask whether or not vitamin-A-tolerance curves were used as a means of following serially such children, who supposedly have a partial pancreatic fibrosis. I think it is important to decide whether this is an entity by itself or merely a phase in the disease.

I am under the impression that some of the children who are said to have normal duodenal juice and subsequently are said to have no trypsin have merely been given an incorrect diagnosis. They may have bronchiectasis with a predominantly Gram-negative flora, perhaps the result of prolonged aerosol or intramuscular penicillin therapy. If, as is often the case, this Gram-negative conversion results in the presence of Pseudomonas aeruginosa, then the swallowed sputum will contain copious amounts of bacterial gelatinase. This may be mistaken for trypsin unless tests on duodenal juice for proteolytic activity make use of the soybean trypsin-inhibitor technique.

My colleagues and I have seen children whose duodenal juice would liquefy gelatin in a dilution within the range of low normal, who subsequently did not have this gelatinase present, and who were found to have no trypsin. We felt they represented not a stage of the disease but merely a laboratory error.

DR. L. EMMETT HOLT JR., New York: Dr. Shwachman has described the gradual disappearance of pancreatic enzymes. I wonder whether he has made any observations on their reappearance. I recall one case seen in Baltimore some years ago in which there was a complete absence of pancreatic juice and a diagnosis of cystic fibrosis was made. The patient was given conventional therapy and returned for observation to the hospital some three years later perfectly normal.

DR. HARRY SHWACHMAN, Boston: I want to answer Dr. Holt's question first. We have not seen enzymes reappear once they are completely absent. In partial insufficiencies, so many factors can operate that one must do serial examinations before one can draw conclusions. An important point I failed to emphasize was that many of our patients had not one but three or four duodenal-fluid assays.

Dr. Johnstone asked many questions, and some of these merit further study before they can be answered adequately. What the viscosity changes are due to is one of these questions. We feel that determination of these changes offers us valuable information. It is so simple to do, requires simple equipment, takes little time, and in the past has often supplied the only abnormal measurement for a child who subsequently showed complete absence of trypsin.

As to the stimulation of the pancreas by olive oil, we think this is a much more physiological method than the introduction of secretin intravenously, which may occasionally produce disastrous effects. Secretin is available, but it is not always easy to get. It is usually not a purified substance, and some children are allergic to it. These facts do not rule out its value as a stimulus for the pancreas. As a matter of fact, 10 years ago we presented a study on the effect of secretin in pancreatic insufficiency and showed that secretin will not cause an alteration

an increase in volume, or an increase in enzyme production of pancreatic juice in patients who have complete pancreatic insufficiency. The fact that bile occurs after administration of olive oil makes us feel that this measures what actually happens when patients digest their food under normal circumstances.

We have done vitamin-A-tolerance curves for some of the patients reported on, and for a few with partial insufficiency normal vitamin-A-absorption curves were obtained.

I think it is clear that in patients for whom serial examinations show progressive changes we are dealing with a dynamic disease. In studying siblings of known patients in whom the disease later developed our earliest observations were made when no clinical manifestations of the disease or laboratory evidence existed.

We have not used soybean inhibitors. We have used a number of separate techniques for determining proteolytic activity. We have not depended upon gelatinase as the only type of proteolytic enzyme. If we did that, we would certainly make many errors. Anyone working in this field has seen patients who were given wrong diagnoses. In closing I want to emphasize that the most important and reliable diagnostic procedure is a study of the duodenal fluid.

Primary Pulmonary Hypertension. Dr. S. Richard Bauersfeld, Alex J. MacDonald, L.R.C.P., S.I., Dr. Morgan Berthrong, and Dr. Helen B. Taussig, Baltimore.

Pulmonary hypertension means that the pressure in the pulmonary artery is abnormally high. The increased pressure in the pulmonary artery may be associated with a malformation of the heart—such as a systemic right ventricle—or it may be due to some abnormality of the pulmonary vascular bed. When its cause lies not in the heart but in the lungs, we have designated the condition as "primary" pulmonary hypertension.

The purpose of this paper is to present the clinical picture associated with primary pulmonary hypertension as seen in five cases in children.

The clinical picture is distinctive. Dyspnea and ready fatigability are the outstanding symptoms. Cyanosis may or may not be present. Feeding difficulty, with failure to gain weight, is also common. The heart is enlarged, there are a systolic thrill and murmur along the left sternal border, and in addition there may be a high-pitched diastolic murmur. The pulmonary second sound is generally loud and split. Terminally there is cardiac failure with engorgement of the liver.

The electrocardiogram shows right axis deviation and right ventricular hypertrophy.

Fluoroscopic examination shows enlargement of both the right auricle and the right ventricle and marked prominence of the main pulmonary artery with increased hilar markings.

The hemodynamic mechanism in this condition is similar to that of pure pulmonic stenosis. The increased resistance in the pulmonary vascular bed increases the pressure against which the right ventricle must work. The increased right ventricular pressure eventually raises the pressure in the right auricle, and when the pressure in the right auricle exceeds that in the left and there is patency of the foramen ovale, a right-to-left shunt will be established and cyanosis will develop. In the cases in which the foramen ovale is closed, cyanosis is absent.

The diagnosis is definitely established by cardiac catheterization, which shows high pressure in the right ventricle and in the pulmonary artery.

At autopsy there was hypertrophy of the right auricle and right ventricle in all cases. The left auricle and left ventricle were normal, as were all the valves. The pulmonary artery was enlarged and thick-walled. In three instances the foramen ovale was patent.

Microscopic examination showed the predominant changes to be in the small muscular arteries. These changes consisted of intimal proliferation and hypertrophy of the media with narrowing of the lumina. In addition there were noted numerous thrombi in varying stages of organization, from completely organized and recanalized fibrotic lesions to those showing only beginning invasion by endothelial cells.

DISCUSSION

Dr. Nelson K. Ordway, New Orleans: The contribution of Dr. Bauersfeld and his colleagues lies, at least in part, in the pointing out of a syndrome which can be recognized clinically and which, as he also points out, can be confirmed by cardiac catheterization. I might add to the diagnostic clinical features the presence of clubbing and the uniform presence

of a precordial bulge. Our group has had experience with four patients with this syndrome. On the basis of the diagnostic criteria that have been described, we were able to make an antemortem diagnosis for three of these, one of whom has not yet come to autopsy.

My comments have to do largely with the interpretation of the cyanosis in these patients. One of our patients was cyanotic and had a slight depression of arterial oxygen saturation which was present also during the inhalation of 100% oxygen, thereby confirming the presence of a small right-to-left shunt which we calculated to be in the order of 12% of the systemic blood flow. Nevertheless, at postmortem examination the cardiac septa were intact; there was no place within the heart that a right-to-left shunt could have occurred.

On the other hand, one of our patients who also had no anomaly within the heart itself except the right ventricular hypertrophy was cyanotic and yet had no evidence of right-to-left shunt or of disturbed oxygenation in the lungs, as shown by normal arterial oxygen saturation. It is clear that the mechanism of cyanosis in his case must have been related to his polycythemia and to marked reduction in venous oxygen content, with a wide auriculoventricular difference, which we demonstrated at catheterization.

Thus I do not think it is possible to predict the presence of an atrial septum defect or patent foramen ovale, even on the basis of a demonstration of a right-to-left shunt.

Where the right-to-left shunt may have been in the patient I mentioned, who was cyanotic, and in another subject who, though not cyanotic also had arterial unsaturation and no patency of the foramen ovale, is a subject for speculation. I rather suspect that in one case it was related to the fact that the pulmonary arterial pressure was greater than the systemic and thus perhaps permitted a right-to-left shunt through anastomotic communication. In the other case possibly the shunt was through dilated bronchial capillaries, which we were able to demonstrate post mortem, although in this case the pulmonary pressure was lower than the systolic.

The authors are to be commended for having eschewed any designation of the syndrome they have discussed. For the past 50 years people have been arguing as to what a certain clinician described. It is certain it is not the syndrome here discussed.

DR. ALEXANDER S. NADAS, Boston: This was an interesting and important presentation. The clinical findings fit into the syndrome that my group has designated within the past couple of years simply as pulmonary vascular obstruction syndrome. It is clinically characterized by right ventricular hypertrophy, with an accentuated pulmonary second sound which, incidentally, in our experience has been a valuable means of differentiating the condition from pulmonary stenosis, which also causes right ventricular hypertrophy. It is not very consistently characterized by pulmonary vascular engorgement demonstrable by x-ray study, including fluoroscopy. If this is considered a clinical syndrome and called pulmonary vascular obstruction, one can say that it may be caused by either a large left-to-right shunt or by the pathological entity of primary pulmonary vascular disease.

It is important when one encounters this syndrome to perform cardiac catheterization to learn the cause. As more and more attempts are made to close left-to-right shunts, patients whose pulmonary vascular obstruction syndrome is caused by shunt can be helped by operation, whereas those whose primary difficulty is in the pulmonary vascular tree are not, as far as I know, amenable to any surgical correction.

I should like to make one comment on Dr. Ordway's remark as to the origin of cyanosis. I wonder whether the patients whom he discussed who had real arterial unsaturation, not correctible by inhalation of 100% oxygen, may not have had an arteriovenous aneurysm in the lungs, establishing communication between the pulmonary artery through the bronchial artery into the systemic artery without actually exposing the blood to aeration in the alveoli. Dr. Sidney Farber in our department has demonstrated such small arteriovenous aneurysms.

DR. GLADYS FASHENA, Dallas, Texas: My colleagues and I have had the opportunity to observe one such patient from the earliest onset of symptoms through autopsy. The interesting thing about this patient was that he had dyspnea but not dyspnea on effort. It was dyspnea in relation to ambient temperature. In the summer he did not have any trouble. When the weather was cool, the minute he walked out of the house he began to have intense dyspnea. I wonder whether Dr. Bauersfeld has any explanation for that phenomenon. It mystified us completely.

DR. S. W. ROYCE, San Marino, Calif.: Last year at these meetings my group had the opportunity of presenting some 20 cases of pulmonary heart disease. In making the diagnosis we were forced to rely entirely on postmortem criteria. I should like to echo Dr. Ordway's gratification that there is now a good clinical way to establish this diagnosis.

I should like to know the width of the anterior wall of the right ventricle in the cases presented today. This measurement, to us, was the best single postmortem criterion for evidence of right heart strain.

DR. S. RICHARD BAUERSFELD, Baltimore: The thickness of the right ventricle was 0.5 cm. in both cases reported.

As to Dr. Ordway's question regarding the mechanism of cyanosis in cases in which the foramen ovale was sealed, I wonder whether there were any capillary changes and also whether the cyanosis had been observed continuously or occurred only in the terminal stages.

I certainly agree with Dr. Nadas' comment that it is most important to distinguish primary pulmonary hypertension from the so-called secondary type of hypertension such as occurs in Eisenmenger's complex, since there is great hope that surgery will offer help to patients with the latter.

In none of our sections were we able to note any fresh thrombi, and at no time did we find evidence of pulmonary arteriovenous fistulae.

I cannot explain why the condition in these patients seemed to vary with the weather. This circumstance is noted in many cyanotic children but is not consistent, since some seem to do better in hot weather and others do better in cold weather.

The striking thing in all of these children was their appearance of relative well-being while they were at bed rest, but as soon as they undertook any exertion they became markedly dyspneic.

Measurement of Carbohydrate Assimilation. DR. OLLI SOMERSALO (by invitation), New York.

Up to the present time it has not been possible to measure carbohydrate assimilation with accuracy. The blood sugar curve is a resultant of several processes. The breakdown of unabsorbed carbohydrate by the intestinal bacteria makes it impossible to assay that fraction and thereby to measure absorption. These difficulties can be avoided by the use of carbohydrates tagged with isotopic carbon, the unabsorbed carbohydrate derivatives being measured by determining the isotopic carbon in the stools.

At the time the present study was commenced the radioactive isotope of carbon, C^{14}, had not been cleared for general use and it was therefore necessary to use the stable isotope, C^{13}, for labeling. By exposure of leaves of the plant *Canna indica* to $C^{13}O_2$ in the presence of ultraviolet light, followed by suitable extraction procedures, a quantity of sucrose labeled with C^{13} was obtained. Clinical studies were carried out on three premature infants with this material. It was found that, in contrast to their impaired fat absorption, they absorbed sugar without difficulty. Observations on the carbon dioxide exhalation curve which were made by means of measurements of the exhaled $C^{13}O_2$ revealed a rapid turnover of the isotopic carbon.

Since December 1951 the Atomic Energy Commission has cleared the radioactive isotope of carbon, C^{14}, for use in limited quantity in normal subjects. These studies are therefore being pursued with carbohydrates tagged with this material. It is hoped by this means to answer a number of questions which have puzzled pediatricians—such as the comparative digestibility of various monosaccharides, disaccharides, and polysaccharides and the effect of various agents upon carbohydrate assimilation.

DISCUSSION

DR. CHARLES D. MAY, Minneapolis: It is most interesting to add this new technique to study of a problem on which further information could not be obtained because of difficulties in measuring absorption of carbohydrate. There is just one question I want to ask the author.

I notice that the doses of this precious material which they were obliged to use were in the order of 95 mg., which may be revealing of the usual physiological path. I wonder whether when they have an opportunity to study the pathology of carbohydrate assimilation, the question of dosage may not prove important; that is, whether a greater load may not be required to reveal dyscrasias in carbohydrate metabolism.

DR. ARTHUR F. ANDERSON, New York: I was impressed with the appearance of counts in the chart a relatively few minutes after the administration of glucose. I wonder whether this is a unique observation which may modify our concepts of exchange following absorption of carbohydrate.

DR. CHARLES A. JANEWAY, Boston: I should like to ask a question which probably reveals ignorance. I wonder whether the author, in his summing up, would mention the situation with regard to the clinical use of C^{14}, which, as I understand it, has a very long half life.

DR. OLLI SOMERSALO, New York: To Dr. May, I should like to answer by saying that we cannot give more than 5 units of C^{14} because that is the upper safety limit established by the Atomic Energy Commission. This dose is small, and we cannot get completely accurate measurements. We hope the dose will be increased.

As to C^{13}, the dose of about 100 mg. gives fairly accurate results.

In normal conditions, I agree that these doses may show insufficient evidence as to absorption, but if absorption is impaired, the reverse may be true. We shall be able to demonstrate the isotope with better accuracy. Those doses were given in larger carrier doses, in about 0.5 gm. of sucrose per kilogram of body weight.

As to Dr. Anderson's comment, we were also very much surprised at the rapid appearance of the isotope. I forgot to mention that in some instances we were able to detect it two minutes after the feeding.

I think I have already answered Dr. Janeway's question about the safety dose of C^{14}. It is established by the Atomic Energy Commission. I think it is based on the fact that this amount is excreted completely in urine in 24 hours.

Growth and Certain Metabolic Features of Infant Macaque Monkeys (Macacus Mulattus) After Thyroid Ablation: I. Growth and Development in Normal Infant Rhesus Monkeys (MM). DR. DONALD E. PICKERING, DR. FRANCIS SCOTT SMYTH, DR. KENNETH G. SCOTT, GERTRUDE VAN WAGENEN, PH.D., and DR. W. MCEWEN, San Francisco.

Growth, as reflected by nitrogen, calcium, and phosphorus metabolism, was investigated in three infant macaque monkeys from birth to 140 days of age. Techniques of metabolic study in infant macaques were presented.

During this period quantities of the selected dietary ingesta were measured, and nitrogen, calcium, and phosphorus balance studies were conducted at selected intervals. The monkeys selectively ingested 375 to 400 cal. per kilogram a day during the first few days of life, and thereafter their intake declined at a new uniform rate until, during the last few days of study, they took in approximately 200 cal. per kilogram a day. A similar pattern characterized the quantity of nitrogen, calcium, and phosphorus ingested.

Initially they ingested approximately 1,800 mg. of nitrogen, 380 mg. of calcium, and 300 mg. of phosphorus per kilogram a day. These quantities declined at a constant rate, and at the end of the study they ingested approximately 1,000 mg. of nitrogen, 200 mg. of calcium, and 170 mg. of phosphorus per kilogram a day.

Growth was characterized by their regaining birth weight at 5 to 10 days of age; stabilization of the rate of body-weight gain at 30 to 40 days, and a gradual decline in the rate of gain thereafter.

The relative proportion of the growth of muscle mass to total body growth during the period of study was determined by serial endogenous-creatinine determinations on each animal. Creatinine excretion was 26 ± 1 mg. per kilogram a day in all animals, regardless of age. This fact strongly suggests that growth is proportionate in muscle, skin, bone, and so on during the period represented. This observation was supported by serial determinations of the Na^{24} space in all three animals studied. Between the ages of 40 and 140 days their Na^{24} space was found to be $36.5 \pm 1.5\%$ of body weight.

Features of nitrogen, calcium, and phosphorus balance during the period of uniform decline in the rate of body-weight gain were presented.

During this period of uniform growth, the macaques studied showed nitrogen retention of approximately 90 mg. per gram of body-weight gain a day. In this growth process they simultaneously utilized calcium and phosphorus at a ratio of 5 mg. of nitrogen to 1.25 mg. of calcium to 1 mg. of phosphorus.

DISCUSSION

DR. HARRY A. WAISMAN, Chicago: These workers seem to be embarking on a worthwhile and longitudinal study. I should merely like to indicate that it would be hazardous, if I understood the speaker correctly, to embark on a long-time program in which the diet is only 12 to 15% protein.

In the use of a synthetic diet in which there is approximately 20 to 22% protein, as in a synthetic diet containing sucrose, casein, and purified vitamins, growth of an older monkey weighing about 1,500 gm. is apparently better than growth of these infant macaques, and I should merely like to suggest that definite attention be paid to protein content for the exhaustive studies the authors are contemplating.

DR. LAWSON WILKINS, Baltimore: I think this is exceedingly interesting and important work, and it brings back an experiment done with monkeys by Dr. Walter Fleischman that I think is of considerable interest (Fleischman, W.; Shumacker, H. B., Jr., and Straus, W. L., Jr.: Influence of Age on the Effects of Thyroidectomy in the Rhesus Monkey, *Endocrinology* **32**:238, 1943).

Before we had other than surgical means of getting rid of the thyroid, Dr. Fleischman and his co-workers thyroidectomized a number of rhesus monkeys, both adult and young ones. Among the adult monkeys he could detect absolutely no changes of thyroid function after removing the thyroid. The monkeys stayed just as active and energetic and enjoyed their sex life and everything else as much as before.

He made detailed studies to eliminate the possibility that there might still be present some aberrant thyroid tissue. Although the technique perhaps is open to some criticism, we fairly well convinced ourselves that there was no accessory thyroid tissue in the adult monkeys and that they got along remarkably well without thyroid.

In the same breed of monkeys, thyroidectomized young became beautiful cretins. I hope some further work will be extended to the adult monkey along the lines that have been indicated.

DR. FRANCIS S. SMYTH, San Francisco: I can only reemphasize some of the features that Dr. Pickering mentioned and those that Dr. Wilkins discussed. Beginning in 1885, Van Horsley performed thyroidectomies in monkeys, and there have been several similar studies. Almost uniformly the monkeys were adults. They were not always of the species described. A great many instances of tetany developed. In the more recent work of Fleischman, Shumacker and Straus, mentioned by Dr. Wilkins, they used nine macaque monkeys, in four of whom tetany developed, and their youngest was 8 months old. It seems to me that we are fortunate in having Element 85, or radioactive iodine, as perhaps eliminating either the oversight of aberrant thyroid tissue or involvement of the parathyroid.

In addition, I think we are most fortunate in having access to this well-controlled colony of Dr. Van Wagenen's in New Haven, Conn., and to start with young animals accustomed at an early age to the laboratory procedure.

DR. DONALD E. PICKERING: I want to thank the discussants for their comments. Dr. Waisman questioned the protein content of the diet employed. Our dietary regimen was designed to allow optimal protein intake and was based upon a review of (1) the protein content of macaque milk, (2) the feeding habits, likes, and dislikes of infant macaques, and (3) the dietary regimen successfully employed in Dr. Van Wagenen's Yale colony. Dr. Wilkins' comments have been discussed by Dr. Smyth.

Role of the Distal Tubule in the Production of a Dilute Urine. DR. CLARK D. WEST, DR. S. A. KAPLAN, and DR. S. J. FOMON, Cincinnati.

Earlier studies have provided indirect evidence of the renal tube process by which urine is rendered hypertonic to plasma. Osmotic diuresis in the hydropenic subject, by whatever solute it is produced, is characterized by a regular relation between the rate of urine flow and the osmotic pressure of the solutes excreted. Within the framework of this relation, widely varying patterns of urine composition appear which are characteristic of the loading solute employed and highly reproducible from experiment to experiment. The strict dependence of urine flow on the osmotic pressure of the solutes excreted, whatever their chemical nature or pattern of distribution in the urine, leads to the assumption that hypertonic urine is produced by the abstraction of water alone from the tubular fluid as it passes through the distal segment of the nephron.

To explain the production of a dilute urine, two hypotheses have been advanced. The most widely accepted hypothesis holds that urine is diluted by the distal reabsorption of approximately one-eighth of the filtered sodium and chloride with a minimum of water. In opposition to this concept stands the hypothesis that urine is diluted by the secretion of water by the distal tubule. To test these two hypotheses the composition of the urine during combined water and osmotic diuresis was studied. If urine is diluted by a radical change in the tubular handling of electrolyte, as is required by the popular hypothesis, the fixed patterns of urine composition produced by the various loading solutes in hydropenic animals should be altered as the urine becomes dilute. On the other hand, dilution of the urine without change in its composition would imply that the tubular handling of electrolyte is not altered by hydration and would lend strong support to the hypothesis that urine is diluted by the distal secretion of water.

Experiments were performed on hydrated dogs in a manner identical with that of previously reported experiments on hydropenic animals except that large loads of water as well as of solute were administered. Despite reduction of urine osmolarity to values of 125 milliosmoles per liter or less and augmentation of urine flow to values three to four times as great as those observed in the hydropenic animals, urine composition was identical in the two groups. The preservation of urine composition under the stress of loading, independently of the osmolarity of the final urine, is best explained by assuming that the process, and hence the site, of tubular solute reabsorption is unaffected by the state of hydration. Thus, in hydration, as in hydropenia, urine composition must be determined by solute transfers occurring in the proximal portion of the nephron and the concentration of the urine by distal transfers of water. Assuming isosmotic proximal fluid, the production of a hypotonic urine can then be ascribed only to the secretion of water by the distal tubule.

DISCUSSION

DR. JACK METCOFF, Boston: I want to call your attention to the use of the term "osmotic diuresis." Osmosis, from which the term is derived, is the process of migration of solvent across a semipermeable membrane. In this case, water migrates from outside the tubule to an area of higher solute concentration in the lumen. If that is the case, then, indeed, the authors have osmotic diuresis and have proved their case.

If, on the other hand, the large quantity of solutes present in the urine after a significant load reduces the escaping tendency of water, it produces a solute diuresis. I believe the authors have produced a solute diuresis.

DR. HENRY L. BARNETT, New York: I think it is of some interest that in Homer Smith's recent monumental book on the kidney he discusses this problem in one sentence, in which he says, "It is hereby assumed that there is no secretion of water by the tubule."

As the Cincinnati group has done so well in the past in challenging existing concepts about kidney physiology, I think the evidence that Dr. West and his group have presented offers good indirect evidence in support of the concept of water secretion. He pointed out, and I think it needs to be reiterated, that this evidence is indirect. However, apart from the observations made by analysis of fluid obtained by micropuncture, all the existing concepts of kidney function are based on indirect evidence. Unfortunately, thus far it has not been possible to obtain fluid directly by micropuncture from the distal tubule.

DR. CLARK D. WEST, Cincinnati: I wish to thank Dr. Metcoff and Dr. Barnett for their comments. Dr. Metcoff and I had quite a discussion of the semantics of the word "osmotic" last night, and I have no quarrel with his reasoning.

I should like to point out that it is becoming clear that there are two distinct types of diuresis, solute, or (as many say) osmotic, and water. The animals in the hydropenic group were undergoing a diuresis solely because they had been loaded with solutes which claimed excretion in the urine. Theirs was a pure solute diuresis. The hydrated dogs, on the other hand, had not only the same load of solute to excrete but in addition a load of water. As a result their urine flows were even greater than in the hydropenic animals and their urine may be considered as a mixture of two components, first a solute component which was identical in composition with that observed in the hydropenic animals and, second, a water component which may be thought of as essentially pure water. The identity of the solute component with that observed in the hydropenic animals indicates that the complex phenomena occurring in the proximal tubule which determine urine composition must have been the same in the two groups. The water

component then must have had its origin independently of the osmotic component and in a manner which does not involve solute transfers. Thus one can best ascribe it to the secretion of water by the tubule.

I am glad Dr. Barnett brought up the point that this is only indirect evidence. I agree heartily. In the absence of elaborate micropuncture studies, the only way the distal secretion of water could be demonstrated directly would be by the attainment of urine flows in excess of glomerular filtration rate. The experimental conditions for such a demonstration could be brought about only through physiological trickery, which we have not as yet mastered.

Observations on the Metabolic and Clinical Effects of Carbonic-Anhydrase Inhibitors in Epileptics. DR. W. H. BERGSTROM (Syracuse, N. Y.), DR. R. F. CARZOLI, DR. C. LOMBROSO, DR. D. T. DAVIDSON, and DR. W. M. WALLACE, Boston.

The administration of drugs capable of inhibiting carbonic anhydrase in the body leads to failure of acid excretion by the kidney. The end-result of the fixed-base loss so occasioned is metabolic acidosis. Sulfanilamide is the prototype drug leading to such inhibition. A sulfonamide now available, Lederle 6063, possesses several hundred times the carbonic-anhydrase inhibitory power of sulfanilamide yet little of the toxic and none of the chemotherapeutic properties of the latter.

The present investigation was undertaken as a study of the feasibility and clinical safety of employing the acidifying effects of this compound for the control of epilepsy. It was hoped that such a method, if effective, would prove superior in clinical acceptability to the use of ketogenic diets.

We have administered the drug to one child with petit mal epilepsy and obtained a complete documentation of the changes in acid-base balance of the body fluids and urine over a prolonged period. The drug has also been given to 42 epileptic patients in an attempt to evaluate its therapeutic effectiveness.

Administration at the rate of 8 mg. per kilogram a day led, in the course of three to four hours, to a 70% inhibition of the whole-blood carbonic anhydrase. Continuation of this rate of administration maintained the initial reduction; doubling the dose produced no further significant effect. Complete inhibition seems impossible. Coincidentally with the initial inhibition the urine became alkaline (pH about 8.0), the rate of excretion of sodium and potassium was doubled over the control period, and the formation of ammonia and titratable acidity by the kidney ceased. Serum total carbon dioxide rapidly decreased to about 20 mEq. per liter and the pH to about 7.2. As long as the drug was given the serum changes persisted; no tendency for increase or decrease of the metabolic acidosis occurred. In contrast to this stability of the body fluids, the urine quickly (one to two days) returned to the control pH (5 to 6) and to the control rate of fixed-base, ammonia, and titratable-acidity excretion. Were this rapid defensive adjustment not made by the kidney, lethal acidosis would presumably result. Such a defensive reaction appears to limit, in many cases, the attainment of marked acidosis.

Clinical trial in 42 patients with intractable epilepsy led to 90 to 100% seizure control in 4 instances and 50 to 90% control in 4 others. None was made worse. There was no correlation between clinical improvement and blood carbonic-anhydrase activity. The dose used was from 10 to 30 mg. per kilogram a day. The dose was increased until either clinical improvement or intolerance appeared. Signs of toxicity which limited the dose were fatigue, flushing, polydipsia, hyperpnea, and complaints of paresthesias or headache. There was no evidence of damage to the kidney or hemopoietic system. Carbonic anhydrase was not more than 70% depressed in any case.

It is apparent that Lederle 6063 is of limited value in the management of epilepsy, serving as a useful adjuvant in a small percentage of cases refractory to other measures.

DISCUSSION

DR. WILLIAM M. WALLACE, Boston: Our initial hope in trying this drug was that it would provide a way to produce acidosis in the epileptic more efficient than the clinically difficult use of ketogenic diets. While therapeutically the trials resulted in little success, the physiological data are of interest.

Dr. Lenox and Dr. Davidson feel that the drug has some value in certain patients. One of these patients was possibly of some theoretical interest. He was a child whose epilepsy took the form of intense periods of hyperventilation. The use of this drug in this rare form of the disease was extremely effective.

The physiological feature that interested us most was the return of the urinary acidity to normal after the initial period of inhibition of acid excretion. This drug is being used extensively to examine the means by which the kidney excretes an acid urine. All these observations have been short term and obviously represent data gathered while the kidney is operating, so to speak, out of equilibrium. I think the data indicate that renal function is not carried out in isolation but show nicely that it adapts its function to changing conditions in the body fluids.

The experiments presented emphasize the need for study of renal function in terms of ultimate adjustment rather than during periods of biochemical imbalance. We originally thought that the data indicated that two mechanisms might be available for acid production by the kidney and that we were seeing the second one brought into action. Dr. Bergstrom's explanation seems a plausible one and brings us back to a more comfortable unitary point of view.

DR. ROBERT COOKE, New Haven, Conn.: I should hate to take away any of the credit from the kidney, but my colleagues and I have been studying the effects of disturbances in acid-base balance on transfer of hydrogen and potassium between the cells and the extracellular fluid, and from this point of view it would be a tremendously complex problem to figure out what happened to the cells in this child during the administration of the drug. From our observations, it would seem that the kidney is more likely to handle what comes to it in the extracellular fluid and that the cell transfers may well have accounted for the changes in the acid-base balance of this child, rather than that there was any sudden change in function or acquisition of new abilities by the kidney.

DR. W. H. BERGSTROM, Syracuse, N. Y.: Our data surely do not permit any assumption regarding cell transfer in this patient, since the study was not planned along that line. The hypothesis offered in explanation of the self-limitation of this acidosis is admittedly probably naive. It is, however, incontestable that the hydrogen ion concentration of this patient's extracellular water must necessarily have risen considerably, as defined by his pH measurement, and it seemed to us not altogether implausible that whatever mechanisms were operating in moving hydrogen ions into the tubular fluid would be facilitated by an increased gradient, that is, by a higher pressure, if one may use that term, on the extracellular-water side of the tubular cell.

Enzyme Studies and Clinical Observations in Congenital Methemoglobinemia. DR. HARRY A. WAISMAN, DR. JULIUS B. RICHMOND, and DR. JAMES A. BAIN, Chicago.

Biochemical and clinical observations were made over a four-year period in a 12-year-old boy who had congenital methemoglobinemia. After the diagnosis was confirmed by spectrographic analysis of the blood, it was found that methylene blue was more effective than ascorbic acid in reducing the methemoglobin back to oxyhemoglobin. It was also found that the ascorbic acid level in the blood had an indirect relationship to the amount of methemoglobin in the blood. The position and shape of the oxygen-dissociation curve were similar to those observed in normal patients. A study of the oxygen-carrying capacity showed a notable increase following the administration of methylene blue intravenously. The rate at which methylene blue was able to reduce methemoglobin to oxyhemoglobin was studied by means of an oximeter, and the administration of 61 mg. of methylene blue intravenously in the form of a 1% solution over a three-minute period converted the methemoglobin to oxyhemoglobin within a five-minute period. The inability to reduce the ferric iron in methemoglobin to ferrous form has been thought to be due to a deficiency of coenzyme factor I in the red blood cells of such patients. The enzyme studies were undertaken to determine by direct means the rate of oxidation and reduction of coenzyme I under a variety of conditions in normal and in methemoglobinemic blood. No "cytochrome-reductase-like" activity in either blood was demonstrated when a manometric method was used. Some doubt has been cast on the validity of the hypothesis that coenzyme I (reduced) reacts directly with the methemoglobin even in normal cells, which are presumably not deficient in the flavoproteins. It is suggested that methemoglobinemia is an inborn error in which a particular enzyme necessary for the efficient reduction of methemo-

globin to hemoglobin is absent in patients with congenital methemoglobinemia, and the point is emphasized that increasing recognition must be given to the fact that such enzyme deficiencies may account for some of the clinical conditions which appear to have no definite etiology at the present time.

DISCUSSION

DR. IRVING SCHULMAN, New York: I think it is very interesting that despite the fact that the basic defect in methemoglobinemia is a failure to convert ferric iron to ferrous, the affected children must have intact similar ferric-ferrous systems. Food iron is in the ferric form, and before absorption takes place it must be converted to the ferrous form in the acid medium of the stomach; in crossing the mucosal barrier of the gastrointestinal tract the iron again becomes ferric; when released to the serum for transport the iron again becomes ferrous. All these complicated ferric-ferrous systems must be intact in children with methemoglobinemia simply because they do not generally suffer from iron-deficiency anemia.

We must also assume that when the red cells containing methemoglobin reach the end of their life span and are destroyed, the ferric iron at some point again becomes ferrous so that it may be reutilized for hemoglobin synthesis. If this were not true the affected growing children would soon have inadequate iron for hemoglobin formation and anemia would be manifest.

It appears, therefore, that the metabolic defect in this disorder is a localized one and is probably limited to the red cell itself.

DR. HARRY A. WAISMAN, Chicago: Dr. Schulman's point is, of course, well taken. This particular boy showed perfectly normal development throughout his now 16 years, and despite the fact that he was cyanotic for a long period, at least 11 years to our knowledge, this condition did not interfere with his normal activity.

The defect in red blood cells may be related to specific genes, as Gibson has shown, and the ability to make the conversion seems to be much more effective with methylene blue than with ascorbic acid. Despite the fact that some patients seem to do fairly well with ascorbic acid, they do much better with methylene blue.

Mean Serum Calcium and Phosphorus Levels in Infants Fed Formulas Containing and Not Containing Vitamin D During the First Weeks of Life. DR. JOSEPH B. PINCUS, and DR. ISAAC F. GITTLEMAN, Brooklyn.

Park, Guy, and Powers and, independently, Kramer and Howland have demonstrated that vitamin D has a regulatory effect upon the serum calcium and phosphorus levels in rats fed diets containing varying amounts of calcium and phosphorus. Albright's experiments on the action of vitamin D led him to conclude that the primary effect of vitamin D is to aid the absorption of calcium from the intestinal tract. Recent investigations seem to corroborate his hypothesis.

Gardner, Gittleman, and Pincus showed that the dietary calcium and phosphorus which the newborn infant receives play an important role in the causation of hypocalcemia.

In the course of these studies we observed that vitamin D seems to aggravate this tendency. In breast-fed babies and those receiving fresh cow's milk with no vitamin D, hypocalcemia did not develop in the first week of life. We therefore decided to study the effect of vitamin D in varying amounts and with various diets on the serum calcium and phosphorus levels in infants during the first week of life.

Nine groups of infants were thus studied: In group 1 there were 41 infants. These received evaporated milk containing 25 units of vitamin D per ounce of undiluted milk. In group 2 we had 17 children. They were fed fresh cow's milk mixtures (four parts of milk to one part of water). This milk contained (undiluted) 400 units per quart.

In group 3, which numbered 18 newborn infants, we gave formulas similar to those used in group 2, but the milk did not contain any added vitamin D. Group 4 numbered 60 infants. They received formulas of powdered milk. In the diluted form this milk contained 400 units of vitamin D per quart. Group 5 contained 60 infants. The formula given was like that given to group 4. No vitamin D was added. Group 6 had 60 infants. They received formulas like those given to the infants in groups 4 and 5, and 600 units of vitamin D (water-soluble) was added to their diets daily.

Group 7 was made up of 17 infants who received breast milk. Group 8 had 18 infants. They were fed breast milk, supplemented with a powdered-milk mixture containing no vitamin D. The infants in group 9 received breast milk but were also given 600 units of dispersible vitamin D orally daily. This group had 13 babies.

Serum calcium and phosphorus were determined on the first day of life and on the day of discharge.

We found that vitamin D in the amounts given had no beneficent regulatory effect on the serum calcium and phosphorus levels. The tendency to hypocalcemia was more marked as the dose of vitamin D was increased. The infants receiving powdered milk with no vitamin D showed 8.3% of hypocalcemia, while the group receiving the same formula with vitamin D showed 16.6% of hypocalcemia. When the dose of vitamin D was increased to 600 units a day the percentage of hypocalcemia rose to 23.3%. Breast-fed infants given vitamin D tended to have lower serum calcium values and higher serum phosphorus levels. This tendency was never observed in any of the breast-fed babies so far studied by us who did not receive vitamin D.

DISCUSSION

Dr. Benjamin Kramer, Brooklyn: This work of Dr. Pincus and Dr. Gittleman, of course, has certain practical implications and some interesting theoretical sidelights.

On the practical side, one might argue that perhaps here is another piece of evidence that breast milk is the preferable food for the newborn infant rather than cow's milk or any preparation derived from cow's milk; or perhaps that the cow's milk mixtures now fed will have to be modified in order to bring about a more ideal relationship between calcium and phosphorus—one which perhaps will lead to a more nearly normal concentration of calcium and phosphorus in the serum.

On the theoretical side, the question of how vitamin D brings about the higher incidence of hypocalcemia is important. Some recent work of Scandinavian observers has shown that vitamin D prepared in the water-soluble form has a marked accelerating effect upon the action of phosphatase in breaking down hexose phosphate and that perhaps in this way vitamin D facilitates the absorption of inorganic phosphorus from the gastrointestinal tract, permits a higher concentration of inorganic phosphorus in the blood plasma, and therefore reversibly reduces the calcium in the plasma.

This work reminds me of the early observations made when ultraviolet light therapy was first introduced, when such therapy often brought a drop in the calcium with a rise in the phosphorus and not infrequently precipitated active tetany.

Another possibility, of course, is that vitamin D has an inhibitory effect upon the parathyroids, which perhaps function in the newborn infant at less than 100%, thus lowering the calcium and tending to increase the inorganic phosphorus in the serum.

Dr. L. Emmett Holt Jr., New York: I should like to bring out the point that the dose of vitamin D is a variable of great importance here. Dr. Kramer has referred to the observations of Huldschinsky, since confirmed by others, that the effect of small doses of vitamin D is initially to raise the phosphorus and secondarily to lower the calcium, sometimes precipitating tetany. On the other hand, when larger doses of vitamin D are given, the initial hypocalcemia does not occur. Both the calcium and the phosphorus rise. Therefore, I wonder whether we should not give larger doses of vitamin D to the newborn.

Dr. Harold E. Harrison, Baltimore: Dr. Holt mentioned that there is an apparent paradox here, since an agent like vitamin D, which ordinarily increases concentrations of calcium in hypocalcemic states, is now being incriminated as causing a reduction of serum calcium in newborn babies.

It is quite true that in the vitamin-D-deficient subject, subtherapeutic doses of vitamin D may cause a temporary drop of serum calcium and a rise of serum phosphorus. On theoretical grounds, that could be easily explained.

In the subject not depleted of vitamin D, however, no such sensitivity to small doses of vitamin D should be expected. These newborn infants are presumably not depleted of vitamin D. The dose they would have received during the first week of life can be calculated and is extremely small. One would have to assume, then, if these figures are correct, that these infants are extremely sensitive to small doses of vitamin D and behave like vitamin-D-depleted subjects, which is a rather unusual idea.

The other possibility is that patients with diminished parathyroid activity—and, of course, newborn babies have been said to have diminished parathyroid activity—are also hypersensitive to small doses of vitamin D. There is no information about the susceptibility of the parathyroidectomized subject to small doses of vitamin D. We all know, of course, that large doses of vitamin D are extremely effective in raising the serum calcium of hypocalcemic subjects with parathyroid insufficiency.

I do not know whether this work has practical implications. Thousands of babies have been given evaporated milk enriched with vitamin D during the first week of life with relatively little clinical damage resulting. I think the theoretical implications are interesting and warrant further exploration of this rather unusual sensitivity of the newborn baby to small doses of vitamin D.

The data as presented are not sufficiently detailed to permit one to draw final conclusions concerning the statistical validity of the differences between groups.

DR. JOSEPH B. PINCUS, Brooklyn: I wish to thank all the discussers and commentators. Dr. Holt's suggestion to give larger doses of vitamin D is well taken. We plan to do that. Our hesitation to do so was based on the fact that when we increased the dose of vitamin D from a range of 25 to 100 units a day to 600 units a day the tendency toward hypocalcemia was aggravated. We are now giving the infants 1,250 units a day, but we have not yet tabulated our results.

Evidence has been accumulating that a state of transient hyperparathyroidism occurs in many newborn infants. Several investigators have suggested that vitamin D and parathyroid hormone are physiological antagonists. It would therefore follow that the administration of vitamin D during the transient state of hypoparathyroidism would aggravate the physiological imbalance. Our demonstration of a greater incidence of hypocalcemia when the dose of vitamin D was increased is evidence in favor of this view.

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

BACTERIAL SENSITIVITIES TO CHEMOTHERAPEUTIC SUBSTANCES. J. C. W. MACFARLANE, Great Ormond Street J. **2**:118 (Dec.) 1952.

Sensitivity tests were done routinely over a period of one year, using blotting paper discs impregnated with the various antibiotics and sulfonamides. These discs were placed about the edge of nutrient agar or blood agar plates, which were inoculated with pure broth cultures. A zone of inhibition of not less than 5 mm. from the edge of the disc indicated sensitivity to that antibacterial agent.

Results indicated that reactions of different bacteria to the antibodies and the sulfonamides have become so marked and so diverse that laboratory controls of chemotherapy for the more serious infections have now become essential.

Tables showing the relative sensitivity of 10 different organisms and various antibiotics and sulfonamides are included.

McGUIGAN, Evanston, Ill.

NEW TESTS AS TO THE ORIGIN OF LACTOBACILLUS BIFIDUS. L. MOSER, Ztschr. Kinderh. **68**:25 (No. 1) 1950.

Lactobacillus bifidus occurs physiologically in the intestines of newborn infants at about the second or third day of life. Various sources for the bacillus and ways by which it may enter the intestinal tract of the newborn have been considered. The author believes breast milk to be the source and proves by means of microscopic slide preparations and cultures the presence of L. bifidus in mother's and cow's milk even before a possible infection of the mother's breast by the infant's mouth can take place. He does not deny that there might be other sources by which infection can take place, such as from the mother's skin, vagina, or anus, or even that the infection might be intra-amniotic.

GLASER, Jerusalem.

Metabolism; Infant Feeding; Milk and Other Foods

BASAL METABOLIC RATE IN OBESE CHILDREN WITH A NOTE ON THE BASAL METABOLIC RATE IN DWARFS. ALBERTA ILIFF, HARRY H. GORDON, HELEN McNAMARA, and W. RANDAL BELL, Pediatrics **4**:744 (Dec.) 1949.

An analysis of the results of 524 observations of the basal metabolism of 348 obese children is presented. Since only 3% of the basal metabolic rates were lower than —15% of the Child Research Council surface area-age standards, it is suggested that these standards can be used satisfactorily in the management of children with obesity. For reasons which are not obvious, these standards do not suffice for children with dwarfism.

FROM THE AUTHORS' SUMMARY.

DEHYDRATION AND ITS MANAGEMENT. M. P. BHAGAT, Indian J. Child Health **1**:7 (Jan.) 1952.

The pathogenesis of dehydration is briefly but very lucidly explained with emphasis on fluid and electrolyte balance. Treatment is discussed in detail, with careful description of the calculation of electrolyte deficiency and the various means of correcting such deficiency.

McGUIGAN, Evanston, Ill.

NUTRITION IN PEDIATRICS. S. C. SHETH, Indian J. Child Health **1**:14 (Jan.) 1952.

In short paragraphs the author discusses the body needs in terms of calories, proteins, amino acids, vitamins, carbohydrates, fats, and water and minerals. The effect of undernutrition on the fetus is mentioned. Separate discussions are included covering the feeding of the normal breast-fed infant and the premature infant. Suggestions are made to improve the nutritional status of Indian children in the future.

McGUIGAN, Evanston, Ill.

INTRAVENOUS USE OF GREEN COCONUT WATER IN PEDIATRICS. N. G. MOJUMDAR, J. Indian M. A. **20**:211 (March) 1951.

The author used green coconut water intravenously in cases of nutritional edema. He injected 100 cc., and edema disappeared after nine days. No untoward reaction was noted.

McGUIGAN, Evanston, Ill.

LIVER DAMAGE IN TOXICOSIS. O. TEZNER, Ann. pædiat. **176**:321 (May) 1951.

In 14 infants with toxicosis the cephalin-cholesterol test and the formol test were done. The formol test was positive in seven cases, the cephalin test in four. After the toxicosis was cured, both tests became negative. It is concluded that damage to the liver plays an important role in the pathogenesis of toxicosis.

FROM THE AUTHOR'S SUMMARY.

FAT TOLERANCE IN INFANTS. W. DROESE, Ann. paediat. **178**:238 (April) 1952.

The present investigation was carried out in order to find out whether the amount of biliary acids and lipase recovered from the duodenum on an empty stomach could be a clinically useful gauge for the recognition of fat intolerance in premature, newborn, and older infants. In all cases in which an addition to the daily intake of buttermilk of 10 to 20 gm. of butter-flour mixture leads, according to Czerny-Kleinschmidt, to dyspepsia, the content of biliary acids in the duodenal juice is reduced, and that of lipase is reduced in some cases. In the light of comparative examinations of the biliary acid and lipase contents and the fat balance, it could be shown that the lowering of the biliary acid and lipase content in the duodenal juice has to be considered as an expression of a generalized secretory disturbance of the digestive glands in consequence of immaturity or damage of the intermediary metabolism.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

RICKETS AND SO-CALLED RICKETS. S. P. BHATTACHARJEE, Indian J. Pediat. **18**:1 (Jan.) 1951.

The author calls attention to the fact that many children in India are thought to have rickets, while actually rickets is rare there owing to the sunshine. The difference between the nonspecific nutritional disorder and rickets is outlined.

McGUIGAN, Evanston, Ill.

THE VITAMINS OF MILK (FROM PEDIATRIC AND BIOLOGICAL POINTS OF VIEW). G. MOURIQUAND, Pédiatrie **39**:157 (No. 2) 1950.

Vitamin C determinations of breast milk showed variations according to the type of food intake of the mother, but in general the quantity was sufficient to prevent scurvy. Vitamin C reserves of the newborn are negligible, and the ability to synthesize is not accepted by most authors. Fresh cow's milk contains less vitamin C than breast milk, its quantity depending also on the cow's fodder, and storage for twenty-four to forty-eight hours, boiling, pasteurizing, and sterilizing produce a loss of 30 to 60% if the milk is not consumed within a short time. If, however, it is stored at low temperatures, most of the vitamin C is conserved. Condensed milk (with or without sugar, powder) contains insufficient vitamin C to prevent scurvy.

The vitamin D contents of breast and cow's milk are small; yet rickets is not seen as much in breast-fed infants as in infants fed cow's milk. The author believes that calcium and phosphorus are more easily absorbed in human milk than in animal milk. The vitamin D content can be raised by irradiating the cows or the milk, by feeding the cows vitamin D, or by adding vitamin D to the milk.

The vitamin A content, too, varies greatly with the type of food intake, and thus with the season, in cow's milk. Skimmed milk and buttermilk are certainly deficient in vitamin A.

Vitamin B seems to be contained in sufficient amounts in breast milk of well-nourished women, but in cases of maternal malnutrition this vitamin is retained by the mammary glands and so deficiencies will appear first in the child and not in the mother.

Milk is a good source of riboflavin, nicotinic acid, and vitamin E. Neither mother's nor cow's milk is a good source of vitamin K. Vitamin F, consisting probably of some nonsaturated fatty acids, is present in the cream.

GLASER, Jerusalem.

OSTEOSCLEROTIC SYNDROME AND OVERDOSAGE OF VITAMINS A AND D. G. FRONTALI, Schweiz. med. Wchnschr. **82**:430 (April 12) 1952.

A 4-year-old girl was treated with streptomycin for miliary tuberculosis of the lungs. In addition, she received 60,000 I. U. of vitamin A and 40,000 of vitamin D per day. She was dismissed after four months. The miliary lesion had cleared, as well as evidence of renal involvement. At home vitamin A medication was continued with a dosage of 150,000 I. U. every second day. About two months later the patient was readmitted. Widespread osteosclerosis, including the cranium, particularly the base, was found. There were retention of nitrogen in the blood, elevation of the blood pressure, hypoisosthenuria, anemia with reduction of erythropoietic activity, and possibly some hepatic lesions. These lesions did not regress as rapidly as the osseous hypercalcification, which on cessation of vitamin A medication disappeared nearly entirely.

AMBERG, Rochester, Minn.

THE ABSORPTION OF VITAMIN A BY RECTUM. LUIGI BARILLA and PIERFRANCESCO PERUZZI, Riv. clin. pediat. **50**:196 (March) 1952.

The authors report the vitamin A blood levels obtained in 10 children from 11 months to 10 years of age after vitamin A has been introduced by rectum. The authors consider this method very useful, having found a quick absorption and therapeutically sufficient drug levels.

FROM THE AUTHORS' SUMMARY.

ANOTHER CASE OF ACUTE BENIGN HYDROCEPHALUS IN AN INFANT AFTER A MASSIVE DOSE OF VITAMIN A. JOSE M. CLUET GARCIA, Acta pediat. españ. **9**:1448 (Dec.) 1951.

The author presents a case of a 3½-month-old child who had the history of ingestion of a massive dose of vitamin A. The child had the usual symptoms of hypervitaminosis A plus meningism, with positive Kernig and Brudzinski reflexes, but without fever. The fontanel was bulging, and there was obvious parietal suture separation. The child recovered without spinal puncture or other treatment and with no apparent sequelae.

The theory is that the hydrocephalus is due to hypersecretion of cerebrospinal fluid, to a defect in the mechanism for reabsorption of this fluid, or to a modification of the fluid pressure of vasomotor or nervous origin.

ALLEN, San Francisco.

Hygiene; Growth and Nutrition; Public Health

EPIDEMIOLOGY OF CHILDREN OF SCHOOL AGE. MEGIAS VELASCO, Acta pediat. españ. **10**:83 (Jan.) 1952.

The author reports the defects found in the examination of 10,800 school children. Various defects, such as tonsillitis, cardiac defects, and defects of eyes and ears, are reported, but most of the study is devoted to the number and stage of the cases of tuberculosis discovered.

ALLEN, San Francisco.

THE IMPORTANCE OF SOCIAL FACTORS IN THE ETIOLOGY OF DYSTROPHY IN THE INFANT. MARIA L. SALDUN DE RODRIGUEZ and JOSE M. PORTILLO, Arch. pediat. Uruguay **23**:89 (Feb.) 1952.

Etiological factors of infantile dystrophy are connected with social conditions; thus 90% of hospital patients suffer from it, but it is exceptional in private practice. Those social conditions, ignorance, poor financial state, bad living conditions, illegitimacy, all lead to a chronic alimentary insufficiency which expresses itself through the disturbed physiology of dystrophy. Different social indices are graphically shown, and the parallelism between incorrect feeding, dystrophy and infantile mortality is pictured.

Purely medical care has little effect on the cure and prevention of dystrophy individually, and in the group. The basic factors already mentioned must also be fought. Good social workers should be trained so that they will be able to make an exact social diagnosis, make constructive use of community resources, or simply train the mother and the family.

Basic knowledge of child rearing and hygiene should be disseminated as the best means for treatment and prevention of dystrophy. Well baby clinics and health centers should be founded or expanded; sufficient and correct nutrition should be secured as well as early medical care in case of illness, and, especially, there is great need of qualified social workers.

FROM THE AUTHORS' SUMMARY.

INCREASE (NOT DECREASE) OF MORTALITY IN VIENNA IN THE THIRD MONTH OF LIFE IN THE YEARS 1948 TO 1951. HERBERT ORAL, Wien. klin. Wchnschr. **64**:355 (May 16) 1952.

The author noted that the mortality of infants in the third month of life in Vienna did not decrease, compared with that of the second month, as in Austria as a whole and elsewhere. It remained the same, or increased. This is brought into relation with the resumption of work away from home by the mothers.

AMBERG, Rochester, Minn.

Prematurity and Congenital Deformities

CONGENITAL CATARACT AND MENTAL DEBILITY. M. SCHACHTER, Pédiatrie **39**:885 (No. 7) 1950.

Five cases of congenital cataract and mental debility are described. In two cases a family history of mental deficiency was obtained, the condition being attributed to constitutional-hereditary factors. The third case history revealed rubeola of the mother during the first months of pregnancy; in one case the mother was syphilitic, and in the fifth child neither hereditary nor exogenous factors could be elicited except premature birth.

GLASER, Jerusalem.

SOME ASPECTS OF PREMATURITY. F. CANIVELL and M. ZAMORA, Arch. pediat. **2**:129 (Sept.) 1951.

The author points out that, although infant mortality rates have fallen very appreciably in the respiratory and gastrointestinal diseases because of better nutrition, antibiotics, and improved sanitary conditions, the deaths due to prematurity have not fallen in the same proportion.

The rate of deaths due to prematurity, however, fell 50% in centers especially prepared for care of the premature as compared with a 21% fall in general hospitals in the United States. These figures were taken for the decade from 1936 to 1946.

The statistics in other countries are also cited. Spain stands between the countries with great decrease in mortality due to prematurity and those with poor records. There is evident need for premature centers.

There is also need for better reporting because, although Spain has fewer premature births per thousand live births, it has a high mortality rate in prematurity deaths among certain socioeconomic groups.

The following topics concerned with prematurity are discussed: (1) prenatal prophylactic measures; (2) factors during gestation; (3) traumatic factors at birth; (4) hemorrhagic factors; (5) injury to the respiratory center, and (6) the anoxia due to these factors plus the poor development of the lung tissue in premature infants.

Treatment is outlined for various conditions causing death due to prematurity.

ALLEN, San Francisco.

CONGENITAL APLASIA OF THE ABDOMINAL MUSCLES. E. MARTISCHNIG, Wien. klin. Wchnschr. **64**:116 (Feb. 15) 1952.

To the 51 reported cases of aplasia of the muscles of the abdominal wall another is added. The theories concerning the genesis of this defect are discussed. The fetal injury is assumed to occur most probably during the second to third week of life.

AMBERG, Rochester, Minn.

BRACHYMESOPHALANGY OF THE FIFTH FINGER. F. SCHMID and F. JUNKER, Ztschr. Kinderh. **68**:399 (No. 4) 1950.

A study of roentgenologic changes of the middle phalanx of the fifth finger showed the frequent association of this minimal anomaly with other more significant anomalies, particularly of the cerebrum. The "accidental" occurrence of this malformation in combination with other malformations is much more frequent than hereditary forms. Damage to the germ plasma occurring during the first three months of pregnancy is considered etiologically. The author points out that this phalanx is the last one of the hand to ossify in the embryo and that the end phalanx of the thumb, which also shows frequent disturbances, is the first one to be ossified.

GLASER, Jerusalem.

RETROLENTAL FIBROPLASIA. J. H. VAN BOLHUIS, Maandschr. kindergeneesk. **19**:17 (March) 1951.

Retrolental fibroplasia is still a rare disease in Holland. A description is given of the clinical picture and pathology of this condition, and different publications, mainly of American origin, are cited on this subject. In the morbid histories of three premature infants (birth weight under 1,280 gm.) wherein the feeding, prophylactic, and therapeutic measures are mentioned, so-called etiological factors, such as overdosage of vitamin A, iron, or emulsifying agents in water-miscible vitamin preparations, could be ruled out.

No answer to the etiological problems could be found in the diet either of the infants or of the mothers. Corticotropin may offer a promising approach to treatment. Systematic examination of the eyes of all premature infants is essential.

FROM THE AUTHOR'S SUMMARY.

Newborn

DIFFUSE ANGIECTASIS OF THE CEREBRAL MENINGES OF THE NEWBORN INFANT. EDITH L. POTTER, Arch. Path. **46**:87 (Aug.) 1948.

An extensive search of the literature has failed to reveal descriptions of vascular abnormalities generalized over the surface of the brain in any age group. Localized increases variously situated are the only ones on record. As far as the author has been able to determine, tumors arising from the meningeal vessels or malformations of meningeal vessels which might be interpreted as angioma or other type of vascular tumor have never been described or observed in fetuses or young infants. The present report concerns three newborn infants whose meningeal vessels all produced a diffuse angiectasis. There was no connection of the vessels to the brain or dura. The vessels appeared to be in the nature of capillaries or terminal veins. In each instance there was also an abnormality of the heart. No specific symptoms led to the diagnosis ante mortem, the infants dying at birth, 24 hours, and 32 hours after birth respectively. The first two cases showed over-all enlargement (hypertrophy) of all the heart chambers; in the third a left innominate vein entered directly into the left atrium.

HAW CHAN, San Francisco.

EFFECTS OF X-IRRADIATION IN NEWBORN RATS. S. P. STEARNER and E. J. B. CHRISTIAN, J. Exper. Zool. **118**:495, 1951.

Newborn rats were exposed to x-rays shortly after birth (one-half to five hours) or at 1 or 2 days of age, with radiation doses ranging from 400 to 1,000 r and exposure rates of 6, 40, and 80 r per minute.

Of the youngest rats 100% died within two weeks after exposure to any dose, and the mean survival time decreased with increasing dose. Approximately 50% of deaths occurred within four days after exposure to 600 r at a rate of 80 r per minute, but the deaths were delayed in the groups exposed at the rate of 6 r per minute. No effect of variation in dosage rate was observed after exposure to 400 and 800 r. However, exposure to 1,000 r produced a shorter mean survival time when delivered at 6 r per minute than when delivered at the

higher rate. The effects of dosage rate upon survival two and four days after irradiation were shown to be significantly different for doses of 600 and for doses of 1,000 r.

While resistance to x-rays increased rapidly during the first two days after birth, no effect of variation in dosage rate upon survival was observed at any dose level tested.

Generalized edema, hyperemia, and renal hemorrhages were prominent autopsy findings at one to two days after irradiation in animals exposed within five hours after birth. The gross changes which occurred later were typical of those that accompany acute radiation deaths. In addition, multiple cerebral hemorrhages developed within one day after irradiation. Cerebellar and medullary hemorrhages appeared after five to seven days, while those in the cerebrum decreased in size and number. The transparent cranial roof permitted direct observation of brain lesions in the living animals. The relation of the autopsy findings to the early deaths is discussed, especially the predilection of the hemorrhages for renal and central nerve tissue.

REID, New Brunswick, N. J. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CONGENITAL MALFORMATIONS OF THE URINARY TRACT IN THE NEWBORN. U. PELLEGRINI and T. BRAIBANTI, Lattante **23**:136 (March) 1952.

Two cases in newborn infants of agenesis of one kidney, a megaloureter on the opposite side, and distended bladder are reported. The cause of this abnormality is to be traced to an early disturbance in embryonic development.

HIGGINS, Boston.

DEVELOPMENT OF ISOAGGLUTININS IN THE NEWBORN INFANT AND THE GROWING CHILD. L. BASSI, Minerva pediat. **4**:38 (Jan. 31) 1952.

Five hundred children, up to 7 years of age, were studied to obtain data on the development of hemagglutinins. In this preliminary report, it is noted that isoagglutinins are practically always absent at birth in the blood of children who develop blood of groups A or B, and frequently absent in the blood of children who later are of group O. Paradoxical isoagglutinins of maternal origin are rarely found in the blood of newborn infants.

HIGGINS, Boston.

ASPHYXIA NEONATORUM. S. FERRAR, Arch. pediat. **2**:115 (Sept.) 1951.

Asphyxia is discussed under several subdivisions, including the mechanisms which start respiration in the newborn and factors which may interfere with this physiological process.

The following factors causing asphyxia are discussed: (1) possible causes of hypoxemia on the maternal side, such as cardiac disease and metabolic diseases; (2) fetal factors such as anomalies, syphilis, erythroblastosis fetalis, and prematurity; (3) factors due to delivery, including prolonged labor and such complications as abnormalities of placenta, cord, or uterus, and complications due to obstetrical intervention.

The injudicious use of anesthesia, hypnotics, analgesics, and oxytocics may also be a factor.

The anatomical pathology and the symptoms, classification, and complications and sequelae are discussed.

Under treatment the author discusses methods of assuring proper drainage of the respiratory tract and the use of oxygen and artificial respiration. Stimulating drugs should be used with caution, and the proper maintenance of heat to the newborn should not be forgotten.

ALLEN, San Francisco.

FAMILIAL OCCURRENCE OF ADIPONECROSIS NEONATORUM. TORBEN JERSILD and AXEL PERDRUP, Acta pædiat. **39**:389 (No. 4-5) 1950.

A case of adiponecrosis neonatorum is described. The maternal side of the patient's family shows a high incidence of similar cases, together with delayed deliveries and high birth weights.

FROM THE AUTHORS' SUMMARY.

SEVERE ANEMIA AND ACIDOSIS IN A NEWBORN INFANT CAUSED BY DEHYDRATION AND RESTRICTED URINE PRODUCTION. CH. DE KRUIJFF, Maandschr. kindergeneesk. **20**:163 (June) 1952.

Severe uremia and acidosis in a newborn infant were caused by dehydration and restricted urine production. Treatment changed the acidosis into an alkalosis, followed by tetany and irregularity of the heart, and the uremia and dehydration completely disappeared. A certain dullness was observed for a long time, possibly due to cerebral injury. This observation is discussed.

FROM THE AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF THE PRICE-JONES CURVE IN HEMOLYTIC DISEASE OF THE NEWBORN. S. I. DE VRIES, Nederl. tijdschr. verlosk. en gynaec. **95**:201 (Jan. 20) 1951.

The author discusses the results of the distribution curve according to Price-Jones of 60 newborn infants (full term, premature, either sensitized by Rhesus antagonism or not) suffering from a manifest form of hemolytic disease of the newborn. On this account the qualitative changes of the curve appear to be of greater significance than the absolute size of the diameter, the dispersion, or the coefficient of variability. These changes do not always correspond with the serological findings in the mild forms of the disease. This is considered to support the opinion that hematological anomalies are sometimes a more subtle reagent than the serological ones.

VAN CREVELD, Amsterdam, Netherlands.

CARE DURING PREGNANCY AND NEONATAL MORTALITY. B. S. TEN BERGE, J. A. F. SCHUT and C. A. G. NASS, Nederl. tijdschr. verlosk. en gynaec. **95**:1480 (May 19) 1951.

An inquiry was made into the causes of neonatal mortality in the Netherlands during one year, 2,465 forms (58%) having been received fully completed. The total number of stillbirths amounted to 4,763 (1.9%), the number of infants dead within five days to 3,268 (1.3 %).

The largest group was that of "congenital anomalies" (667 out of 2,775). Closer study of the causes is highly important. The group "intoxication, eclampsia" was considerable (432 out of 2,775). It was stated that weight, blood pressure, and urine are not yet regularly checked in all pregnant women. "Unknown and premature without specification" is a group of 1,032 out of 2,775.

The examination on Rh factor has not yet been carried through sufficiently. From statistics it appears that the influence of age and order of four diagnostic groups as compared with a check group corresponds with the clinical findings. These groups are Rh, syphilis, prematurity, and intoxication. An arrangement of the statistical data better suited for clinical usage is suggested.

VAN CREVELD, Amsterdam, Netherlands.

CONCENTRATION OF PROTHROMBIN AND PLASMA ACCELERATOR GLOBULIN IN THE BLOOD OF NEWBORN INFANTS. S. K. TENG, Nederl. tijdschr. verlosk. en gynaec. **95**:3222 (Nov. 3) 1951.

In healthy mature infants, the plasma accelerator globulin (AC globulin) levels showed no differences from those obtained in older children and adults. The prothrombin concentrations determined with a "two-stage" method were always lower than in older children and adults. There were fewer variations in the values obtained with the "two-stage" technique than usually are found with a "one-stage" method.

In the blood of a patient with melena neonatorum, and probably present already before birth, were a physiological hypoprothrombinemia and a low level of plasma accelerator globulin. The bleeding disappeared as the plasma-accelerator-globulin content rose.

The melena neonatorum in this case was primarily due to the low plasma-accelerator-globulin level. The physiological lowering of the concentration of the prothrombin may have contributed to the hemorrhagic diathesis of this child.

VAN CREVELD, Amsterdam, Netherlands.

A Combination of Disturbances in Development in the Umbilical Region. J. Hage, Nederl. tijdschr. verlosk. en gynaec. **95**:3636 (Dec. 1) 1951.

The author describes the case of a newborn boy with persisting ductus omphaloentericus with exvagination of oral and aboral ileum, a strangulating rest of probably the omphalomesenteric artery, and an omphalocele.

Treatment consisted in operative reposition, cleavage of the cord, ileocecostomy, and reinserting the open end of the ductus into the umbilicus. In the second instance, the open Meckel diverticulum was resected, ileum and abdominal wall being closed.

van Creveld, Amsterdam, Netherlands.

Acute Contagious Diseases

Mechanism Involved in Polyneuritis as Exemplified by Post-Diphtheritic Polyneuritis. M. R. Brown, Ann. Int. Med. **36**:786, 1952.

Because the cause of postdiphtheritic polyneuritis is known, Brown made a survey of 53 affected patients in an effort to understand the mechanism involved in 40 patients with a polyneuritis of unknown origin, but similar to the postdiphtheritic type in its clinical manifestations, spinal-fluid changes, and autopsy findings.

Postdiphtheritic polyneuritis in these 53 patients was remarkably consistent in its course. There was weakness of the palate about 10 days after the acute infection. About four to five weeks later the patient experienced numbness and tingling of the arms and legs, and the deep reflexes were lost. Seven to eight days after these symptoms peripheral sensory loss and weakness of the extremities, and even of the trunk muscles, followed. At the same time, other cranial-nerve paralyses developed in about two-thirds of the patients. The nerves to the eye muscles were particularly susceptible to the diphtheria toxin.

The spinal fluid exhibited the Guillain-Barré syndrome of an increase in protein without an increase in cell count.

The clinical and spinal fluid findings in these 53 patients with postdiphtheritic paralysis were compared with those in the 40 patients with polyneuritis of unknown origin. Of these 40 patients, 13 had had an infectious disease; 12 had diabetes; 1 had dermatomyositis, and 2 had received injections of animal proteins.

Brown believes it is likely that an allergic response of the nerve cell to a foreign substance is involved in both the polyneuritis due to diphtheria toxin and that of unknown cause. In that case, if used early in the course of the disease, corticotropin or cortisone should be effective in both diseases.

Alpers, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

The Present Status of Tracheotomy in Bulbar Poliomyelitis. Robert E. Priest, Lawrence R. Boies, Neill F. Goltz, L. Ian Younger, and Robert L. Koller, Ann. Otol. Rhin. & Laryng. **60**:468 (June) 1951.

According to Priest and co-authors, 26 papers on the subject of tracheotomy in cases of bulbar poliomyelitis have been published since 1946. These are reviewed and discussed. While varying opinions are expressed in these writings, most of the authors favor tracheotomy in certain instances. Secretional obstruction to the airway is recognized as a prime indication, but pharyngeal paralysis alone is thought not to be a proper indication for the operation. Inability on the part of the patient to clear his own airway of secretions, pharyngeal distortion resulting from paralysis, and mechanical obstruction are cited as additional indications.

Some authors advise against tracheotomy on the grounds that the operation is dangerous and mutilating. Others believe that its early utilization prevents some brain damage by assuring more adequate oxygen supply during the course of the disease.

Priest and co-authors state their position based on their own experience, as well as that of others, as follows in summary: 1. Tracheotomy should be done early when needed. 2. Done properly, it adds little risk to the patient. 3. The mutilating nature of the procedure has been overexaggerated. 4. Tracheotomy contributes greatly to prognosis when the patient cannot clear his own airway. 5. Transtubal humidified oxygen under pressure is an important form of

adjuvant therapy. 6. There are no hard and fast indications for tracheotomy. 7. The operation should be done only if other methods of clearing the airway of obstructive secretions have failed. 8. Tracheotomy has a limited, but important, place in the treatment of bulbar poliomyelitis.

STEELE, Kansas City, Kan. [A. M. A. ARCH. OTOLARYNG.].

MYOCARDIAL CHANGES IN POLIOMYELITIS. VERA B. DOLGOPOL and MARY D. CRAGAN, Arch. Path. **46**:202 (Sept.) 1948.

Clinical evidence of myocarditis in poliomyelitis has been reported since 1913. Microscopic evidence has been recognized only since 1941. This report attempts to establish the incidence of acute myocarditis in poliomyelitis as occurring in the Willard Parker Hospital. Pathological material from 92 patients was examined; 91 patients were either in the acute or the convalescent state, and 1 patient was considered as having chronic involvement. Sixteen cases of acute myocarditis were found (17.4%). This figure is lower than that recorded by other observers and might be explained by the fact that only one section was available for study in some of the cases. Multiple sections are frequently necessary to reveal the scattered focal changes. The duration of poliomyelitis in the cases with myocarditis ranged from 2 to 10 days, and in the majority of them (12 cases) did not exceed 5 days. In most of them clinical signs of myocarditis were observed between the second and the fifth day of the illness. The age of the patients varied from 13 months to 37 years. Death from cardiac failure was recorded clinically in four cases. In two other cases the clinical picture was only suggestive of cardiac damage. In all cases, bulbar and spinal involvement were seen microscopically.

HAW CHAN, San Francisco.

SECOND ATTACKS OF POLIOMYELITIS: REPORT OF A CASE WITH AUTOPSY FINDINGS. A. L. HOYNE, and I. LIPTON, J. A. M. A. **146**:707, 1951.

Hoyne and Lipton report a second, and fatal, attack of poliomyelitis in a woman aged 31, with autopsy findings. As a consequence of the first attack, five years previously, the patient had severe weakness of the left lower extremity with moderate atrophy. As expected, at autopsy there was evidence of a past pathologic process, consisting of moderate atrophy of the left anterior horn in the lumbar portion of the cord, and microscopic examination revealed extensive destruction of the nerve cells.

The second attack terminated in death due to respiratory failure four days after the onset of symptoms.

Microscopic examination of the cerebral cortex showed intense congestion of the overlying meninges. The central ganglia showed marked engorgement throughout. There was a large focal extravasation of blood near the left lateral ventricle. About this area was pronounced diffuse infiltration of round cells and leucocytes, and many of the ganglion cells had disappeared or exhibited moderate neuronophagia. Most of the vessels were surrounded by round cells. The dentate nuclei of the cerebellum showed slight engorgement. The ganglion cells appeared intact. There was slight diffuse infiltration of round cells and leucocytes. A few vessels had small collars of round cells. The pons and medulla were conspicuously engorged. Most of the ganglion cells appeared intact. Throughout the tissue there were moderate diffuse infiltration of round cells and a few focal collections of leucocytes. Most of the vessels were surrounded by collars of round cells. There was pronounced congestion of the entire spinal cord and meninges. The cervical and thoracic portions of the cord were notable for the disappearance of most of the ganglion cells from the anterior horns. The gray matter exhibited marked diffuse infiltration of round cells and leucocytes, and the white matter also showed slight infiltration. Most of the vessels of the gray matter and some of the vessels of the white matter were surrounded by collars of round cells and leucocytes. Changes in the lumbar portion of the cord were more accentuated, especially on the left side. A few foamy cells were present in the anterior horns. An absence of ganglion cells was noted on the left side. The few remaining ganglion cells on the right side exhibited pronounced satellitosis and neuronophagia, and a few showed myelination. Collections of round cells were prominent about the posterior roots.

The authors suggest that second attacks of poliomyelitis are due to an immunologically different strain, against which the patient has no previous immunity.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

AUREOMYCIN TREATMENT OF DIPHTHERIA AND DIPHTHERIA CARRIERS. SAMUEL KARELITZ, HARRY KING, and IRA S. RUBINSTEIN, J. Pediat. **39**:544 (Nov.) 1951.

Most strains of Corynebacterium diphtheriae are susceptible to easily obtainable concentrations of penicillin. Patients with acute diphtheria are therefore given antitoxin and penicillin. Over 75% of diphtheria carriers can be cleared with penicillin. Aureomycin in doses of 25 to 50 mg. per kilogram of body weight also is effective against C. diphtheriae. It may be used with antitoxin in acute diphtheria and may be particularly useful against penicillin-resistant strains in the carrier state.

MACDONALD, Pittsburgh.

THE TREATMENT OF PERTUSSIS WITH AUREOMYCIN, CHLORAMPHENICOL AND TERRAMYCIN. LOUIS WEINSTEIN, RAYMOND SELTSER, and C. T. MARROW, J. Pediat. **39**:549 (Nov.) 1951.

Aureomycin, chloramphenicol, and terramycin have added little to the treatment of pertussis. They have little or no effect on symptoms of the acute disease. Removal of Hemophilus pertussis from the respiratory tract and prevention of secondary infections is accomplished best by terramycin, although results are not completely satisfactory.

MACDONALD, Pittsburgh.

SECOND ATTACKS OF ACUTE ANTERIOR POLIOMYELITIS. A. T. COFFEE and W. D. PAUL, Neurology **1**:461, 1951.

Although admittedly rare, the occurrence of a second attack of paralytic poliomyelitis in the same person is unquestionable. The authors summarize 49 previously recorded cases of second attacks of acute anterior poliomyelitis and add 1 case of their own. In the case reported here two distinct attacks were separated by an interval of 24 years.

Coffee and Paul point out that the occurrence of additional symptoms, or the extension of previously existing motor impairment during the few months immediately succeeding an initial attack of acute anterior poliomyelitis, should be considered a recrudescence of existing infection. New symptoms occurring two or more years after the initial episode should be considered a reinfection.

Factors responsible for the occurrence of second attacks of poliomyelitis are as yet little understood. Possible explanations for the occurrence of several attacks of poliomyelitis are cited: 1. A second attack may be produced by a strain of virus antigenically unrelated to that which produced the initial infection. 2. Certain strains may fail to stimulate tissue or humoral antibody production. 3. Certain persons may be incapable of antibody production. 4. The body may lose its immunity in the course of time and therefore become susceptible to reinfection with a homologous strain. Any one or a combination of these factors may be operative in an individual case.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

POLIOMYELITIS VIRUS IN BLOOD OF ORALLY INFECTED MONKEYS AND CHIMPANZEES. DOROTHY M. HORSTMANN, Proc. Soc. Exper. Biol. & Med. **79**:417 (March) 1952.

Cynomolgus monkeys and chimpanzees were given Brumhilde type (Egypt), Lansing type (Y-SK), or Coxsackie virus by mouth, and blood was withdrawn from the femoral artery or vein 24 hours later and again five to seven days later. Tests for virus were carried out by intracerebral inoculation. Seven of ten monkeys and three of four chimpanzees were found to have a viremia early in the incubation period. In some animals the viremia persisted four to six days after the virus ingestion. Virus was not isolated from blood specimens collected during the first three days or after the seventh day.

HANSEN, Galveston, Texas.

PARALYTIC POLIOMYELITIS FOLLOWING INJURY. A. BLAIR HARRINGTON, Lancet **1**:987 (May 5) 1951.

Harrington reviewed the records of 100 unselected cases of poliomyelitis acquired during service in the armed forces, in 5 of which there was evidence that trauma had preceded the paralysis. In four of the five cases the disease appeared within 5 days of the injury, in the

fifth case, within 11 days. In each case the paralysis appeared in muscles closely related to the site of trauma, the injuries being mostly to the lumbosacral region, with subsequent poliomyelitic involvement of the legs. The author states that apparently trauma upsets the balance between the virus and the host and precipitates the disease.

MADOW, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

POLIOMYELITIS IN BOMBAY. G. COELBO, J. Indian M. A. **20**:207 (March) 1951.

The author describes an epidemic of poliomyelitis with 512 cases. A brief discussion of the current theories of epidemiology and the treatment used is included.

McGUIGAN, Evanston, Ill.

OBSERVATIONS ON THE 1950 POLIOMYELITIS EPIDEMIC IN ISRAEL. W. FOLK, Harefuah **21**:7, 1951.

During 1951, a total of 1,600 cases of poliomyelitis was seen in Israel. The height of the epidemic was in June. Only 1% of the patients were Arabs. The disease was severest in adults who had immigrated from the Netherlands and the United States. Most of the patients were from the North; 60% were males; 93% were 5 years of age or under; 56% were 2 years of age or under, and 30, or 7.4%, were reported to be below 6 months of age. Nineteen were 5 months of age or less. One case was that of an infant, 17 days old, whose mother had the disease at the same time. No difference of susceptibility was observed between infants who were breast fed and those who were artificially fed. There was no difference between children who were well nourished and those with malnutrition. No instances of a second attack were reported. Only two sibling pairs were affected in this series. In three cases the infection apparently took place while the child was in the hospital. No case of paralysis appeared in a limb which had recently been vaccinated. Eighty-seven patients had no paralysis. Prodromal symptoms, usually lasting two or three days, were noted in two-thirds of the cases. Paralysis was found twice as frequently in the lower limbs as in the upper limbs. The deltoid was the muscle most frequently involved in the upper limbs. In the lower limbs the muscles involved most frequently were the tibialis anterior, the peroneus, and the quadriceps. In 22 cases the only manifestation of poliomyelitis was facial paralysis. In 34 cases facial paralysis was present with bulbar or spinal paralysis. No changes were found in the electrocardiogram in any of the cases, although autopsy revealed myocardial involvement. In 9% of the cases the spinal fluid contained less than 10 cells per cubic millimeter; in 40%, 20 to 100 cells; in 1%, over 1,000 cells. The highest cell count was 2,515. The total protein of the spinal fluid was higher in cases of severe paralysis. The blood cell count was normal in all cases. In 10 to 15% of the patients admitted with the diagnosis of poliomyelitis, some other disease simulating it was found. Of 51 deaths, 26, or 13.2%, occurred in the first 24 hours. The greatest mortality was in infants. Forty-two of the patients had to be put in respirators; 67% of these died. The mortality in the cases of bulbar involvement was 67%. The author notes that quarantine did not seem to diminish the number of cases or protect persons from contracting the disease. None of the medical or nursing personnel became ill with poliomyelitis. The author stated his disappointment with the use of drugs for reduction of spasms. He prefers the application of heat. He warns against the use of tubes in patients who cannot swallow. He prefers prolonged intravenous feedings, avoiding in this way the danger of vomiting and aspiration. Tracheotomy was performed in eight patients, three of whom recovered.

N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

GERM CARRIERS IN WHOOPING COUGH. M. LUST, Pédiatrie **39**:561 (No. 5) 1950.

By nasopharyngeal swabs and culture on Bordet-Gengou medium with penicillin the author has found Hemophilus pertussis in children in contact with pertussis patients but themselves showing no symptoms, and in children who had had pertussis and had recovered from it. On account of this study, the author suggests revision of the quarantine regulations and extension of immunization.

GLASER, Jerusalem.

THE ACTION OF THE RUBELLA VIRUS ON THE HUMAN FETUS. G. TONDURY, Helvet. paediat. acta **7**:105 (April) 1952.

In this study the effect of rubella virus on the human embryo is described. Six human embryos of different ages were studied whose mothers had been attacked by rubella between the 35th and the 51st day of pregnancy. According to the author's observations, the rubella virus penetrates from the maternal blood stream through the intact chorioepithelium. Consequently the human embryo is not affected by a generalized disease, but only certain organs —the lens, the epithelium of the inner ear, and the enamel organs—are infected, and a destructive effect results. An evident organ affinity exists.

The destruction consists in an admixture in the form of drops and vacuolar variation of the cytoplasm with subsequent pyknosis of the cell nucleus. It does not appear at the same time in the above-mentioned organs. Seventeen days after the mother has contracted the disease, the lens fibers show degeneration, whereas not until 222 days after the mother has been infected with rubella do the sensory cells of the inner ear and the cells of the enamel organs show degenerative changes.

The author assumes, on the basis of his observations, that the virus attacks the epithelial cells of the lens, the auditory vesicle and the enamel organ in premature embryonic state and increases therein. It becomes evident only when the cells have reached their state of differentiation, which is connected with great metabolic activity. With regard to this fact the effect of the rubella virus is phase-specific. It probably interferes with the metabolism of the cells and produces the hyaline droplets of the cytoplasm and the cellular pyknosis.

FROM THE AUTHOR'S SUMMARY.

THE VALUE OF THE CLASSICAL METHODS OF ELECTROSTIMULATION FOR DETERMINING, IN CHILDREN WITH EPIDEMIC POLIOMYELITIS, WHETHER A PARALYSIS, NOTED EARLY WILL ULTIMATELY DISAPPEAR. CL. BÉRAUD, Lattante **23**:129 (March) 1952.

Experience in the Debrousse Hospital in Lyons indicates that about 30% of the children with poliomyelitis having paralysis in the early stage of the disease will later have recovery of muscle function. These cases may be identified by testing the muscle response to faradic stimulation in the early stages of the paralysis; in those cases showing an active response there will be a rapid return of muscle function.

HIGGINS, Boston.

EPIDEMIOLOGY OF POLIOMYELITIS. G. CLOVERO and F. PEREZ GALLORDO, Acta pediat. espań. **9**:1169 (Oct.) 1951.

The author discusses the epidemiology of poliomyelitis in sections on the distribution and elimination of the virus from the infected patient or animal, also on healthy carriers of the virus and on the portals of entry.

Certain conditions are believed to favor the development of the disease, such as avitaminosis A and B, pregnancy, tonsillectomies, and dental extractions.

Epidemics depend, in a manner which is not entirely clear, upon the presence of a population which has not been immunized. Many adults who have never apparently had the disease possess antibodies, and yet children do not unless they have had the disease. How are these antibodies acquired? There are, no doubt, different strains, for troops of American soldiers stationed in the Near East and India had the disease 10 times as often as troops native to these lands. Other epidemics in South Africa and the Island of St. Helena suggest the introduction of a "stranger" among the viruses usually found in these places.

The methods of transmitting virus discussed include transmission by human carriers, from whose nasopharyngeal secretions the virus may be isolated; transmission from feces, from the water supply, and from foods contaminated with the virus by human carriers, and transmission by flies, which seem to be the only insect remotely connected with poliomyelitis.

The history of epidemics in various parts of the world is described. The relationship between potable water, the decline of typhoid in some countries, and the increase in poliomyelitis in these countries after the decline of typhoid are mentioned.

There is a discussion of the forms of poliomyelitis, the incidence in families and institutions and in laboratories where research workers are exposed to virus, the factors of age, sex, and race, and urban versus rural incidence.

The human virus, that of encephalomyelitis of the rat (Teiler's disease), and that of Teschen's disease in the hog are compared in detail; rats and hogs are thought to be reservoirs of the virus between epidemics.

The discovery of similar viruses or mutations by Dalldorf and Sickles, and also the work of Melnick, Shaw, and Curnen are briefly described.

Considerations of the prophylaxis and need for more research end the paper.

ALLEN, San Francisco.

CLINICAL MANIFESTATIONS OF ACUTE ANTERIOR POLIOMYELITIS. G. ARCE, Acta pediat. españ. **9**:1194 (Oct.) 1951.

The author says that the name acute anterior poliomyelitis is inappropriate and proceeds to show the various classifications by many different writers. He devotes most of his time to the commonest type, the spinal type.

The validity of the nonparalytic and the abortive type is discussed, and it is pointed out that only the isolation of the virus in each case can be said to demonstrate the presence of the abortive type. The presence of the virus in healthy adults further complicates the argument.

Some time is devoted to the types of lesions found in the tissues of the nervous system and to the question whether the damage to the nervous system or some metabolic changes in the muscle cause the early spasm. According to Knapp, there may be circulatory lesions producing local anoxia; the liberation of acetylcholine may affect nonmyelinated nerve endings, and medullary anoxia may occur with spasm following the anoxia.

Much of the paper is devoted to diagnosis and signs and symptoms for the testing of all muscle groups for paralysis. The signs described include the sign of Ruhrah, the tripod sign, and Wickman's sign. The sign of Bresevor and Slesinger, which is the displacement of the umbilicus as the forerunner of later paralysis, is useful in cases in which abdominal pain is puzzling.

The prodromal fever graph is described; its value or lack of value as a diagnostic point would seem to be dependent upon the presence of an epidemic. The laboratory findings are also sometimes equivocal.

Finally, the relation between the motor symptoms and the later atrophy is not always evident. Severe paralysis may be followed by slight atrophy or slight paralysis may be followed by severe atrophy.

Doring attributes all the atrophy to vasomotor lesions; Zellwezer and Morf state that the answer to the atrophy will be found in deficient tissue nutrition.

ALLEN, San Francisco.

CLINICAL FORMS OF POLIOMYELITIS. C. ARCE, Acta pediat. españ. **9**:1225 (Oct.) 1951.

In a previous article Dr. Arce discussed the spinal type of poliomyelitis, which accounts for 80% of all cases. In the present article he deals with other clinical forms, including abortive, meningeal, the preparalytic, the neuritic or polyneuritic, and the bulbar.

The diagnosis of the bulbar type, which depends upon the nucleus affected, is elaborated in detail. The facial nerve nucleus is the most commonly affected. The progressive ascending form, commonly called Landry's paralysis, is very serious, often fulminating and fatal. The type called encephalitic, the form which affects the pyramidal tracts, the cerebellar form, and the transverse myelitis forms are also described. The disease in all forms is rare among children under 6 months, but occasionally may be seen. In the cases studied by the author in an epidemic in Santander, there were 63 cases, with 2 in children under 6 months. Forty of the cases were spinal. The list is itemized according to site of the paralysis.

Laboratory diagnosis must confirm the clinical findings. The differential diagnosis must distinguish the disease from many mild upper respiratory and gastrointestinal infections. Even in the period of early paralysis, the differential diagnosis is not simple unless there is an epidemic which causes early suspicion.

Among diseases confused with poliomyelitis are acute rheumatic fever (polyarticular type), sepsis, and acute osteomyelitis. When symptoms are abdominal, poliomyelitis may be confused with appendicitis, peritonitis, or intestinal obstruction.

The meningeal irritation which may occur will also be confused with various types of meningitides and acute infections which are accompanied with meningism. Meningitis caused by virus infection may be very difficult to distinguish, especially the lymphocytic choriomeningitis of Armstrong.

The differential diagnosis must also be made between encephalitic infections and poliomyelitis.

Other rarer conditions which may be confused are polyradiculitis of Guillain-Barré-Sthrall and traumatic lesions which have been overlooked and which may cause limitation of motion in certain muscle groups because of fractures, distortions, hemorrhage in the muscle, etc. Sometimes obstetrical paralyses may simulate poliomyelitis. The pseudoparalysis of Parrott may simulate a peripheral paralysis.

Bulbar poliomyelitis must be differentiated from lesions due to any other factor which causes obstruction of pharynx or esophagus, either of an infectious nature or due to foreign bodies.

ALLEN, San Francisco.

THE TREATMENT OF POLIOMYELITIS. JOSÉ LUIS ALDECOA JUARISTI, Acta pediat. españ. **9**:1247 (Oct.) 1951.

The author reviews the treatment of poliomyelitis in various countries and discusses the treatment at various stages of the disease. The treatment must be individualized and dependent upon the area involved, whether spinal or bulbar.

Usual antibiotics and chemotherapy are not efficacious; gamma globulin and convalescent serum may be; the rest of the treatment is symptomatic and directed at sequelae.

The author discusses muscle spasm and the use of Kenny treatment and the older methods which were somewhat similar. The use of exercises in warm water, electrotherapy, diathermy, and the drugs to prevent ischemia is also included. Surgical intervention later is also discussed.

The treatment is far from satisfactory, but this is no excuse for shunning the task. The need for better facilities in Spain and an organization to fight the disease conclude the discussion.

ALLEN, San Francisco.

TREATMENT OF SCARLET FEVER WITH PENICILLIN. FLORENCIO BOZAN, RAUL CERONI, and JORGE HUBERMON, Acta pediat. españ. **9**:1443 (Dec.) 1951.

This is a reprint from the *Archivos Argentinos de Pediatria*, May, 1950. Two hundred patients were treated with 1,500,000 units of penicillin in the first days of illness. Streptococcus throat cultures were positive in 97% of the cases on entrance to the hospital. The course of the illness was shortened, there was less fever, and the complications were fewer. In the group treated with 1,500,000 units of penicillin there were no cases of nephritis; four cases of nephritis were found in a similar number of cases in which only 600,000 units were used, and five cases among the number who received no antibiotic. The cultures from the throat also showed negative results in a shorter time after the use of the larger dose of the antibiotic.

ALLEN, San Francisco.

SMALLPOX IN THE PREMATURE. RAUL ORTEGA and GUILLERMO REPETTO, Rev. chilena pediat. **23**:108 (March) 1952.

Of 10 premature infants of different ages and weights exposed to hospital contagion of smallpox (alastrim), 3 caught the infection, 2 of whom were over 3 months old. Among the seven exposed who did not fall ill, only one was over that age. The course of the disease was benign. The evolution of temperature was rather unusual.

FROM THE AUTHORS' SUMMARY.

POLIOMYELITIS AND TONSILLECTOMIES. M. COHN, Rev. otorrinolaring. **11**:39 (Aug.) 1951.

Cohn evaluated all the pros and cons on this much disputed subject in a thorough review of the literature. A careful analysis of 560 cases of poliomyelitis in the Children's Hospital in Santiago, Chile, showed only one case in which poliomyelitis was preceded by a tonsillectomy. He believes the following: (1) that it has not been proved that tonsillectomies done in the summer months predispose to poliomyelitis; (2) that recent tonsillectomies in polio patients is an unimportant finding; (3) that of the total number of tonsillectomized children poliomyelitis develops in only a very insignificant number (when this occurs the bulbar form is more prevalent than others); (4) that a morbidity of poliomyelitis in Chile is below epidemic figures, and (5) that postponement of this type of operation in the summertime is not justified except when the morbidity of poliomyelitis reaches epidemic proportions in certain areas, and at that time all elective operations should be avoided.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

DIPHTHERIA. ABELARDO BRENES IBARRA, Pediat. Américas **9**:301 (July) 1952.

There were 1,529 patients with diphtheria admitted to the Infectious Diseases Department of the Hospital San Juan de Dios (San Jose, Costa Rica) in the nine-year period between 1942 and 1950. The total mortality was 7.25%, but it has been between 4.67% and 5.64% since 1947.

A group of 217 personally observed cases, in which there were only 3 deaths (1.38%), is analyzed. Such a low rate of mortality is explained by the fact that all the patients were over 12 years of age. The two sexes were affected with the same frequency. The infection was predominantly localized in the pharynx or tonsils in an overwhelming majority of the cases (97%). Only 3% of the cases were of laryngeal diphtheria; such a low percentage is explainable, as such location is particularly frequent in children under 5 years of age and the author's group includes patients over 12 years of age only.

The most important complication observed in the group was myocarditis; it appeared in 4 cases (1.84%) and was responsible for the 3 deaths among the 217 patients. Pneumonia appeared in 2 cases (0.92%) and acute nephritis in 1 case (0.46%). The results obtained with penicillin and drugs associated with the diphtheria antitoxin are presented. The author and his associates have gathered the impression that neither the penicillin administered intramuscularly nor the sulfonamide drugs given orally had any definite effect upon the usual course of the disease; however, they apparently diminished the frequency of complications due to superimposed secondary infection, with a reduction in the mortality rate. Nevertheless, when the penicillin was locally administered along with the diphtheria antitoxin given by the parenteral route, the average duration of the disease was shortened (from six to four days), faster bacteriologic negativity was achieved (three days instead of five), and the number of convalescent carriers was reduced (from 10% to 5%).

Active immunization of all the children in the preschool and school ages is recommended, as well as all the contacts. The use of combined diphtheria and tetanus toxoids with pertussis vaccine is advantageous in children, since tetanus and whooping cough are also frequent in Costa Rica.

FROM THE AUTHOR'S SUMMARY.

INFANTILE PARALYSIS. VICTOR ESCARDO Y ANAYA, Pediat. Américas **9**:354 (Aug.) 1951.

The author makes a comparative study of the epidemics of infantile paralysis in the Western Hemisphere. The first part comprises Central and South America. He reviews the general aspects, without going into details, to investigate the possibility of establishing some bond or relation between the progress of the illness in the different countries. To this end he presents the morbidity and case fatality rates, with data obtained from the best available sources, but which the author presents provisionally, so that by verifying or correcting these data it should be possible to reach really valid conclusions.

In the second part, the author continues the description of the epidemics of infantile paralysis in the Western Hemisphere, so as to complete the picture of the whole continent. His intention has been only to give a broad view, which, with more data and more accurate conclusions, will make a contribution toward the knowledge of the serious problem of the spread of the disease.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF PERTUSSIS IN INFANCY WITH BLOOD TRANSFUSION. F. J. NIESERT, Deutsche med. Wchnschr. **75**:679 (May 19) 1950.

Repeated intraperitoneal blood transfusions were given in 200 cases of infantile pertussis, half of which during the first three months of life. It was possible to cut short the whooping cough and also to prevent its spread.

AMBERG, Rochester, Minn.

EPIDEMIOLOGY OF INFANTILE DIPHTHERIA. J. STRODER and H. NIGGEMEYER, Deutsche med. Wchnschr. **75**:926 (July 14) 1950.

The increase in the number and severity of cases of diphtheria in infants, observed in various European countries, has been related by some authors to the increased general morbidity of mothers. It cannot be related, however, to a decrease of transmitted antibodies. Various factors are considered, but it is concluded that at present the knowledge of infantile diphtheria is very inadequate.

AMBERG, Rochester, Minn.

HOW LONG DOES IMMUNITY DUE TO ACTIVE DIPHTHERIA IMMUNIZATION LAST? G. PASCHLAU, Deutsche med. Wchnschr. **75**:951 (July 14) 1950.

In a heavily infected region 99% of the immunized preschool and school children were protected against diphtheria for five years, while 18% of the nonimmunized acquired diphtheria.

AMBERG, Rochester, Minn.

PROPHYLAXIS AGAINST SCARLET FEVER WITH PENICILLIN. F. K. FRIEDERISZICK, Kinderärztl. Praxis **18**:117 (No. 3/4) 1950.

Thirty-seven children who were closely exposed for one to two days to scarlet fever received a total of 200,000 units of penicillin over a period of two days. All patients had normal throat cultures in two days, and in only two patients did scarlet fever occur six and seven days respectively after the discontinuation of penicillin. The author feels that effective prophylaxis against scarlatina on this basis is possible; that, however, it does not protect against reinfection after discontinuation of the prophylactic administraton of penicillin. Prophylaxis could be simplified by the use of depot penicillin instead of three-hourly injection. Oral penicillin he considers ineffective according to reports from the literature.

GLASER, Jerusalem.

THERAPY OF SEQUELAE OF POLIOMYELITIS ANTERIOR ACUTA. A. M. LORENTZ DE HAAS, Nederl. tijdschr. verlosk. en gynaec. **95**:1158 (April 14) 1951.

As we do not possess any causal therapy for acute anterior poliomyelitis of any practical importance, controlling the residual symptoms is most important. A description is given of the procedure in the Wilhelmina Hospital in Amsterdam, where the patient, after discharge from the department of infectious diseases, enters into the coordinated charge of physical therapeutist, neurologist, and, orthopedist.

There is nothing essentially new in the therapy applied here as well as elsewhere. The often more encouraging results as compared with those of former years are due to cooperation and to the intensity of the pains taken. The salutary influence of the latter and of the group therapy on the patient's psychic condition may be compared with that observed at the time in Panegrossi's treatment of patients with Parkinson's disease (paralysis agitans) and Parkinsonism.

VAN CREVELD, Amsterdam, Netherlands.

FAVORABLE RESULTS FROM ACTIVE IMMUNIZATION AGAINST WHOOPING COUGH IN A COUNTRY DISTRICT. B. M. VEENLAND and H. R. VAN DER MOLEN, Nederl. tijdschr. verlosk. en gynaec. **96**:431 (Feb. 23) 1952.

In 9 out of 228 children vaccinated prophylactically with the whooping cough vaccine of the Government Institute for Public Health (this vaccine was compared with the Canadian vaccine prepared by the Connaught Laboratories) whooping cough occurred. However, in none of these children had the immunization been complete. The occurrence rate was significantly lower in the vaccinated children than in the nonvaccinated family contacts.

VAN CREVELD, Amsterdam, Netherlands.

THE PREVENTION OF POSTVACCINAL ENCEPHALITIS. W. G. SILLEVIS SMITT, Nederl. tijdschr. verlosk. en gynaec. **96**:554 (March 8) 1952.

The author discusses the possibility that the occurrence of postvaccinal encephalitis is related to an endogenous predisposition. He discusses the possibility of establishing the existence of this predisposition, the so-called neuropathic constitution. The necessity for a flawless and conscientious vaccinating technique is stressed.

VAN CREVELD, Amsterdam, Netherlands.

DECREASING MORTALITY FROM WHOOPING COUGH IN INFANCY. J. E. MINKENHOF and M. W. VAN DER KOOI, Nederl. tijdschr. verlosk. en gynaec. **96**:598 (March 15) 1952.

The authors do not think it likely that chloramphenicol and aureomycin will influence the course of uncomplicated whooping cough. These antibiotics may have a splendid effect against secondary bronchopneumonia resistant to sulfonamide drugs, penicillin, and streptomycin. Since 1948 infants without pneumonia have received dihydrostreptomycin prophylactically.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

METASTATIC HYPERNEPHROMA OF THE BRAIN FROM A NEUROSURGICAL POINT OF VIEW. T. P. STÖRTEBECKER, J. Neurosurg. **8**:185, 1951.

A series of 19 cases of metastatic hypernephroma (carcinoma of the kidney), occurring among a total of over 3,000 cases of brain tumor, is presented. The frequency of hypernephroma among the metastatic brain tumors is about 13%. Metastasis to the brain appears in most cases to be solitary.

Patients can live for several years after extirpation of metastatic hypernephroma of the brain; one patient is still alive 14 years after the operation on the brain. The prognosis appears to be most favorable in those cases in which the primary tumor in the body has been diagnosed earlier and removed, e. g., by nephrectomy, before symptoms manifesting cerebral metastasis appear.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ROENTGEN MANIFESTATIONS OF ACUTE AND HEALED TOXOPLASMIC ENCEPHALOMYELITIS. WYNTON CARROLL, Radiology **54**:554 (April) 1952.

A patient 2 weeks old was admitted to the hospital because of intermittent convulsions of 24 hours' duration. There was no evidence of intracranial calcifications, but many monocytes in the spinal fluid contained phagocytosed erythrocytes, suggesting the possibility of Toxoplasma. At microscopic examination, numerous Toxoplasma organisms were found in the brain and lung tissues.

A second patient, aged 5 years, showed numerous areas of calcification scattered throughout both cerebral hemispheres. At the age of 3 years the patient had had convulsions but showed no gross abnormalities on physical examination later.

ANSPACH, Chicago.

A WIDESPREAD INFECTION OF DOUBTFUL ETIOLOGY. J. RITCHKEN and M. GELFAND, South African M. J. **26**:115 (Feb. 9) 1952.

In a two-part article the authors describe detailed diagnostic, clinical, and epidemiological features of an obscure infection affecting large numbers of children in South Africa during 1951. The illness was characterized by marked pallor, fleeting joint pains, recurrent abdominal pain, prolonged fever, elevated erythrocytes sedimentation rate, and negative physical findings. Recovery was slow but complete after many months. No physical findings were noted other than pallor, irritability, and unremarkable cervical adenopathy.

Laboratory tests revealed generally a normal blood picture, elevated sedimentation rates, negative agglutinations, negative Paul-Brunnell tests, and normal urine and stool examinations. Sulfonamides, penicillin, and terramycin had no effect.

No diagnosis was possible. It was felt that these children suffered from a new virus disease. No virus studies were made, but all bacteriologic tests showed nothing significant.

McGUIGAN, Evanston, Ill.

HYDATID CYST IN PERITONEUM WITH BILHARZIAL INFILTRATION OF ITS FIBROUS WALLS. OSMAN SOROUR, SAMI GUIRGUIS, and SEDDIK A. HALIM, J. Roy. Egyptian M. A. **34**:171 (No. 3) 1951.

A case of hydatid cyst in the peritoneum of a 14-year-old girl is reported. The wall of the cyst contained bilharzic ova.

McGUIGAN, Evanston, Ill.

URINARY TUBERCULOSIS IN CHILDHOOD. J. CIBERT and J. PERRIN, Pédiatrie **39**:77 (No. 1) 1950.

In 33 cases observed by the authors, it was noted that urinary tract tuberculosis increased in frequency toward puberty and that in 34% of the cases the disease was bilateral. The diagnosis is difficult because of the scarcity of symptoms and can be made best by urinalysis and intravenous urogram. Therapeutic results are usually bad, since the disease progresses, causing cystitis and damage to the second kidney. Streptomycin improves the surgical outlook because it leads to more rapid healing of the mucosa and may prevent septic spread.

GLASER, Jerusalem.

A MENINGITIC SYNDROME AND HYSTERIA IN A CHILD WITH ASCARIDIASIS. P. DE ANGELIS, Pediatria **60**:63 (Jan.) 1952.

A 9½-year-old orphan girl with hilum tuberculosis and a patent interventricular septum defect, while under hospital observation, developed a change of personality, which was followed by meningeal symptoms—headache, vomiting and opisthotonus. Lumbar puncture yielded a clear fluid under pressure, with 50 cells, equally divided between lymphocytes and polynuclear cells; the Pandy and Wassermann tests were both negative. Thirteen days after relief of the meningeal symptoms, symptoms of hysteria with catalepsy appeared, lasting for several days. It is possible that the whole clinical picture may have been due to ascaridiasis.

HIGGINS, Boston.

ACTION OF ADRENALIN ON EOSINOPHILIA OF PARASITIC ORIGIN. LUIS BARRERAS, JUAN M. LABOURDETTE, and PÉREZ RUANO, Rev. cubana pediat. **23**:300 (May) 1951.

Seven children with high eosinophile counts due to parasitic infestation were studied by means of eosinophile counts before and four hours after epinephrine injection. The eosinophile counts before the injection ranged from 779 to 3,480 per cubic millimeter. In two cases there was better than a 60% drop in eosinophiles after injection of epinephrine; in one, a 45% drop; in two a 30% drop, and in one only a 19% drop.

NELSON, San Francisco.

ACUTE INFECTIOUS LYMPHOCYTOSIS. U. GREIFELT, Kinderärztl. Praxis **18**:105 (No. 3/4) 1950.

A 3-year-old child became sick with fever, abdominal pains, and a leucocyte count up to 64,000 with up to 90% lymphocytes. Fever and abdominal pains disappeared within a few days, but the lymphocytosis persisted for four weeks. Liver, spleen, and lymph nodes were not enlarged.

In the discussion of the differential diagnosis the author considers whooping cough, infectious mononucleosis, rubella, virus pneumonia, epidemic hepatitis, and lymphatic leukemia. He considers the differentiation of leukemia most difficult and points out that the absence of splenomegaly, lymph node swelling, anemia, thrombocytopenia, and pathologic lymphocytes is often not enough and that only the benign course of the disease permits definite differentiation.

GLASER, Jerusalem.

ANTIHYALURONIDASE CONTENT OF SERUM IN CHILDREN SUFFERING FROM HEMOLYTIC STREPTOCOCCAL INFECTIONS, RHEUMATIC FEVER, AND OTHER DISEASES. MARIE R. H. STOPPELMAN, Acta pædiat. **39**:510 (No. 6) 1950.

The serum antihyaluronidase content in 705 children was determined. The mean titer increases with age. The serum antihyaluronidase content in children suffering from rheumatic fever was compared with that in children suffering from hemolytic Streptococcus infections

and with the titers in children of the control group. The titer was generally high in children with rheumatic fever in the acute phase of the disease. A decrease in the titer was observed when the patients recovered, and a further decrease was mostly seen during the period of chemoprophylaxis.

Three only out of the 11 patients who were in the acute phase of the disease had antihyaluronidase titers which were above the highest values found in the other groups.

No definite conclusions can be drawn, owing to the small number of cases of rheumatic fever. The impression was gained, however, that the determination of the serum antihyaluronidase content may be of diagnostic value in rheumatic fever, but will not provide the diagnostic proof.

FROM THE AUTHOR'S SUMMARY.

AN EPIDEMIC OF BORNHOLM DISEASE IN THE NORTHERN PART OF AMSTERDAM. L. FAÇEE SCHAEFFER, Nederl. tijdschr. verlosk. en gynaec. **95**:2938 (Oct. 6) 1951.

During the summer of 1951 there was an epidemic of pleurodynia in Tuindorp Oostzaan, the northern part of Amsterdam; 358 cases were seen. The Laboratory of Hygiene, Amsterdam University, isolated a virus of the Coxsackie group, type "Powers."

Complications were pleurisy and a special form of angina (herpangina).

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

VARICES, CONGENITAL SYPHILIS, TUBERCULOSIS AND SECONDARY TUMORS OF THE ESOPHAGUS. JAN F. MAJERANOWSKI, Arch. Path. **45**:608 (May) 1948.

All esophagi examined by the author were of adult patients except in cases of congenital syphilis. In seven cases of infants the serologic tests for syphilis were positive. In none were there visible esophageal lesions, but in four of the seven cases histological studies revealed significant inflammatory changes interpreted as syphilitic.

HAW CHAN, San Francisco.

TOXIC EFFECTS OF STREPTOMYCIN COMPOUNDS WITH SPECIAL REFERENCE TO DEAFNESS. D. H. GARROW, Great Ormond Street J. **2**:133 (Dec.) 1951.

Study of complications of streptomycin therapy shows a marked incidence of damage to the hearing apparatus. In the author's hospital prior to January, 1950, 44 patients with tuberculous meningitis and 15 with miliary tuberculosis were given streptomycin sulfate or chloride for four months or longer. One of the surviving meningitis patients is deaf. Five patients with tuberculous meningitis and one with tuberculous peritonitis were treated with dihydrostreptomycin sulfate. Two of the meningitis patients and the peritonitis patient became deaf.

The author points out that onset of deafness is acute and may appear without warning even after treatment has been discontinued. He feels that dihydrostreptomycin is contraindicated for prolonged treatment and that streptomycin sulfate is the drug of choice.

McGUIGAN, Evanston, Ill.

INTRATHECAL TUBERCULIN IN TUBERCULOUS MENINGITIS. A. P. FLETCHER, Lancet **2**:290 (Aug. 18) 1951.

After the report of Smith and Volum on the intrathecal use of tuberculin in treatment of tuberculous meningitis, these authors suggesting that part of the benefit of this agent might be the result of fibrinolytic action on the cerebrospinal exudate, Fletcher treated five patients with tuberculous meningitis who had responded poorly to conventional therapy with intrathecal injections of tuberculin. The results suggested that tuberculin treatment, instead of causing the lysis of exudate, may have contributed to its formation. In two cases fresh blocks developed during treatment; in a third a transient subtentorial block probably developed, and in two considerable progress of optic nerve atrophy occurred during treatment.

MADOW, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SYPHILITIC OSTEOMYELITIS OF SKULL IN INFANT. M. A. LASSRICH, Ann. pædiat. **176**:115 (Feb.) 1951.

This is a report of a case of congenital syphilis in an infant of 4 months with considerable syphilitic manifestations in the organs. Syphilitic osteomyelitis of the skull was observed clinically and roentgenologically during most of its course. Cure was obtained with acetarsone (stovarsol®) and penicillin.

FROM THE AUTHOR'S SUMMARY.

THE ACTION OF MEASLES IN STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS. A. AKKOYUNLA, Helvet. paediat. acta **7**:180 (April) 1952.

Modified measles developed during streptomycin treatment in five cases of tuberculous meningitis. The author believes that streptomycin inhibits the growth of the measles virus and recommends that children with tuberculosis who have been exposed to measles be prophylactically treated with streptomycin.

FROM THE AUTHOR'S SUMMARY.

THE TRANSITORY ICTERO-ASCITIC SYNDROME IN THE TUBERCULOUS CHILD. BERNARDINO PISO, Ann. ital. pediat. **5**:37 (Feb.) 1952.

In a child 17 months old with subacute miliary tuberculosis with perifocal pulmonary reaction and constitutional thymolymphatic symptoms there was suddenly an acute episode of icteroascitic syndrome with serious general involvement and a subsequent quick and complete regression after penicillin, streptomycin, and dietetic therapy.

The author discusses the mechanism of both phenomena, suggesting that their origin may be associated with hepatocellular condition with involvement of the portal trunk and of the choledochus of probably glandular nature; he does not exclude, however, the possibility that the biliary ducts may be involved.

FROM THE AUTHOR'S SUMMARY.

CHANGES IN THE BLOOD PROTEIN AND CHOLESTEROL IN CHILDREN OF VARIOUS AGES FOLLOWING VACCINATION WITH BACILLE CALMETTE GUERIN (BCG). R. DE LUCA and L. SCARCELLA, Lattante **23**:154 (March) 1952.

The blood cholesterol and blood protein were found to have increased 60 days after a group of children and infants had been vaccinated with BCG. By this time, each of the subjects had a positive reaction to the Mantoux test. The increased cholesterolemia was in the cholesterol ester fraction and the increased proteinemia in the beta and gamma globulins. The older the child and the greater the dose of BCG given, the greater was the increase in these immune elements of the blood.

HIGGINS, Boston.

ACTINOMYCOTIC PNEUMONITIS WITH CEREBRAL ABSCESS. M. GENESI, Minerva pediat. **4**:39 (Jan. 31) 1952.

A girl of 10 years was admitted to a hospital with what was believed to be pulmonary tuberculosis and meningitis. She died the next day. Postmortem examination revealed that the pathology was due to pulmonary actinomycosis with a metastatic abscess in the left occipital lobe of the brain.

HIGGINS, Boston.

SKIN TESTS WITH TOXOPLASMIN IN THE PROVINCE OF SASSARI. A. FOIS and C. VULLO, Pediatria **60**:44 (Jan.) 1952.

Skin tests with Toxoplasma antigen were made on 405 children in Sassari; some of the children were well and others hospital patients with various illnesses; none of the tests proved positive.

Tests on 390 patients in a mental hospital yielded 26 positive reactions. Although all 26 also had positive serum reactions, none of them showed the typical eye findings of toxoplasmosis. Definite association of the mental illness with Toxoplasma infection was not possible. It has been noted in mental hospitals that the percentage of positive reactors to Toxoplasma antigen increases with the age of the patients.

HIGGINS, Boston.

VITAMIN A ALONE AND ASSOCIATED WITH STREPTOMYCIN IN THE TREATMENT OF EXPERIMENTAL MILIARY PULMONARY TUBERCULOSIS IN RABBITS. SEVERINO PEDONE and ORESTE BRUNO BARTOLI, Rivista clin. pediat. **50**:98 (Feb.) 1952.

The authors have studied the action of vitamin A on miliary pulmonary tuberculosis experimentally produced in rabbits.

While the animals treated with vitamin A all survived, though without reaching clinical recovery, all animals which had received no treatment died in a short while.

In the autopsy of these animals, done at different intervals, the authors found tuberculous alterations initially serious, with a slow tendency toward recovery.

The authors experimented with the use of streptomycin with vitamin A. They point out the utility of such association; the animals killed at a later date attained clinical recovery, with tuberculous lesions histologically reduced in number and with a productive tendency to heal. The satisfactory results from the use of streptomycin, described by them in an earlier paper, were improved and achieved more quickly when vitamin A was also used.

The authors can therefore affirm that streptomycin is the basic drug in the therapy of miliary pulmonary tuberculosis of the rabbit and that vitamin A has also an important task; that is, to hasten the action of the antibiotic and to stimulate the defense of the organism.

FROM THE AUTHORS' SUMMARY.

BLOOD AND SPINAL FLUID LEVELS AND URINARY ELIMINATION OF 4,4-DIAMINODIPHENYLSULFONE IN ETHYL OLEATE SUSPENSION IN SUBJECTS AFFECTED WITH TUBERCULOUS MENINGITIS. MICHELE PARADIOS and LUIGI BARILLI, Riv. clin. pediat. **50**:122 (Feb.) 1952.

The authors report on the blood and spinal fluid level and urinary diminution after intramuscular injections of 4,4'-diaminodiphenylsulfone ethyl oleate suspension in 5 patients affected with tuberculous meningitis. Doses went from 6 to 8 mg. per kilogram of weight.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF CONGENITAL SYPHILIS WITH PROCAINE PENICILLIN IN AQUEOUS SOLUTION. ALBERTO DE CÓRDOVA, Rev. cubana pediat. **23**:159 (March) 1951.

Ten patients with congenital syphilis were treated. Nine were children 1 year of age or under, and one was a 3½-year-old child. Aqueous procaine penicillin-G was given in a total dose of 100,000 to 230,000 units per pound of body weight divided into equal daily parts given over a period of 10 to 15 days. Three patients were cured, and in four others the results were satisfactory. One child died during treatment; another was lost to the study, and the result in another case was uncertain because of death six months after treatment.

NELSON, San Francisco.

SERUM PROTEINS AND SEDIMENTATION RATE OF RED BLOOD CORPUSCLES IN TUBERCULOSIS OF CHILDHOOD UNDER TREATMENT WITH STREPTOMYCIN AND PARAAMINOSALICYLIC ACID. RUDI THURAU, Deutsche med. Wchnschr. **75**:940 (July 14) 1950.

The serum protein fractions were determined by means of practical precipitation with sodium sulfate, the total protein by means of the Kjeldahl nitrogen determination. In cases of hilus gland tuberculosis in which the state of nutrition was excellent, some decrease of the albumin fraction was noted and a high gamma globulin value, indicating good resistance. Five infants with tuberculosis who were treated with streptomycin were examined, as well as five patients with tuberculous meningitis associated with miliary tuberculosis who were also treated with streptomycin, and five children with tuberculosis who were treated with paraaminosalicylic acid. In the first group of infants the sedimentation rate dropped, the total blood protein increased, the heightened alpha and beta globulin fractions receded, and gamma globulin increased quite decidedly. In the group with tuberculous meningitis the albumins increased, alpha and beta globulins receded, and the gamma globulins did not show a uniform response. With paraaminosalicylic acid treatment the gamma globulins increased regularly with diminution of the increased alpha globulins. A special effect of these two substances on the serum proteins was not evident.

AMBERG, Rochester, Minn.

BRONCHOSCOPY IN PRIMARY TUBERCULOSIS OF LUNG. G. M. H. VEENEKLAAS, Maandschr. kindergeneesk. **19**:29 (March) 1951.

Modern anesthetic technique has led to great advances in bronchoscopy in children. Direct results of bronchoscopic treatment of bronchial abnormalities in primary pulmonary tuberculosis are scarce. The late results are unknown, the expectations uncertain, and the indications indefinite.

FROM THE AUTHOR'S SUMMARY.

PLEURISY OF TUBERCULOUS ORIGIN AND LUNG TUBERCULOSIS. B. VAN VLIET, Nederl. tijdschr. verlosk. en gynaec. **95**:684 (March 3) 1951.

During an observation period varying from 8 to 11 years, the author followed the course of 136 pleurisy patients who entered the Groningen Welfare center. Twenty-one (i. e., 15%) contracted tuberculosis in one form or another; the literature usually gives higher figures. Men and women suffered from pleurisy in equal numbers. The height of the blood sedimentation rate may perhaps have some significance with regard to prognosis; the quantity of the exudate may not, however. Griep's finding (1941) could not be confirmed, that only those in whom already at the time of the pleurisy lung foci are present on the photomicrograph get lung tuberculosis later on. With a view to the seriousness of the syndrome, prophylactic vaccination with BCG is insisted upon.

VAN CREVELD, Amsterdam, Netherlands.

TOXOPLASMOSIS IN THE NETHERLANDS. J. D. VERLINDE and O. MAKSTENIEKS, Nederl. tijdschr. verlosk. en gynaec. **95**:2050 (July 14) 1951.

Among 172 patients suspected of toxoplasmosis, Toxoplasma was repeatedly demonstrated in the ventricle fluid of 7 newborn infants suffering from congenital toxoplasmosis and in the blood of 4 of the patients, during a period varying individually from 6 to 199 days after birth. The development of cytoplasm-modifying and complement-fixing antibodies and their significance for diagnosis are discussed. A positive dye test (titer below 1:100) was found in 63% of 853 serums of persons not suffering from toxoplasmosis; the highest percentage of positive serums occurred in adults.

VAN CREVELD, Amsterdam, Netherlands.

REPORT ON PATIENTS SUFFERING FROM TUBERCULOUS MENINGITIS, TREATED WITH STREPTOMYCIN IN THE NETHERLANDS DURING 1947. W. VAN ZEBEN, Nederl. tijdschr. verlosk. en gynaec. **95**:3214 (Nov. 3) 1951.

In the Netherlands, 104 patients were treated with streptomycin for tuberculous meningitis during 1947. Extensive information on the course of the disease and on the subsequent therapy was collected on 92 patients. In 84 of those, the diagnosis was confirmed bacteriologically or by postmortem examination; 50 of the patients died; 34 have survived more than three years after the beginning of the treatment. Most of the patients (72%) died within six months after the onset of the therapy.

One of the surviving patients had a relapse more than three years after the first attack of meningitis. One suffered severe mental impairment and has convulsions. The remaining 32 patients are leading a normal life, although 3 show residual neurological symptoms (transverse lesion, hemiparesis), while 10 are entirely deaf. The origin of the deafness probably is connected with the dosage of the streptomycin in intrathecal administration.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF OTITIS MEDIA TUBERCULOSA AFTER ORAL ADMINISTRATION OF BCG. E. HAMMELBURG, Nederl. tijdschr. verlosk. en gynaec. **95**:3498 (Nov. 24) 1951.

A case of tuberculosis of the middle ear occurred in an infant to whom BCG was given orally during the first week of life. The origin of this tuberculous inflammation of the middle ear is discussed. It is possible that the BCG bacteria caused the forming of tuberculous tissue in the middle ear.

VAN CREVELD, Amsterdam, Netherlands.

THE SIGNIFICANCE OF DIET RICH IN CALORIES FOR THE TREATMENT OF THE NEPHROTIC SYNDROME. E. E. TWISS, Nederl. tijdschr. verlosk. en gynaec. **95**:3579 (Dec. 1) 1951.

The hypoproteinemia present in the nephrotic syndrome leads to disagreeable symptoms (anorexia, decreased resistance to infections) which in their turn lead to aggravation of the existing negative nitrogen balance. Dietary treatment of this condition requires not only an adequate quantity of proteins, but above all a sufficient number of calories; otherwise the body would consume its own proteins to meet its energy requirement. In order to feed the patient with sufficient calories, a diet relatively rich in fats and carbohydrates should be prescribed. A description is given of some patients who improved with such a dietetic regimen.

VAN CREVELD, Amsterdam, Netherlands.

THE GLUCOSE METABOLISM IN TUBERCULOUS MENINGITIS. I. LEUSEN and K. VUYLSTECK, Nederl. tijdscshr. verolsk. en gynaec. **96**:90 (Jan. 12) 1952.

From a comparative study of the sugar content of blood and spinal fluid in 79 cases of tuberculous meningitis, the authors conclude that in these patients the glucose level of the spinal fluid does not interfere with the carbohydrate metabolism.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels, and Spleen

THE IMPORTANCE OF PATENT DUCTUS ARTERIOSUS IN INFANTS. R. F. ZIEGLER, Am. Heart J. **43**:553 (April) 1952.

A correlative analysis of clinical and laboratory data has been made in a group of 22 infants from the age of 6 weeks to 3 years with uncomplicated patent ductus arteriosus.

Observations are cited which are believed to support a number of important conclusions, among which are the following: 1. The diagnosis of uncomplicated patent ductus arteriosus can be made clinically at any age. 2. Diagnostic findings, such as the type of murmur, systemic blood pressure, and heart size, are analyzed and explained in terms of physiological data. 3. Some of the most important factors in differential diagnosis of congenital cardiovascular defects in infants are outlined. 4. Reasons are given for believing that an uncomplicated patent ductus arteriosus may be and frequently is a serious defect in infancy. 5. Surgical results in this group of infants support the belief that operation can be done safely and successfully in the age group under consideration.

FROM THE AUTHOR'S SUMMARY.

AN UNUSUAL MECHANISM OF SUDDEN DEATH IN CONGENITAL HEART DISEASE. F. F. ROSENBAUM and F. C. STILES, Am. Heart J. **43**:573 (April) 1952.

The authors report two cases. The first was a case of pulmonary atresia, tricuspid stenosis, and patent ductus arteriosus. A thrombus developed in the isolated segment of the main pulmonary artery and obstructed the flow of blood through the ductus into the branches of the pulmonary artery. The second case showed aortic and mitral stenosis, patent ductus arteriosus and atypical coarctation of the aorta. A thrombus formed in the aorta just distal to the aortic valve, obstructing the flow of blood into the innominate and left common carotid arteries.

Thrombus formation must be kept in mind as a cause of sudden death in patients with congenital heart disease.

GIBSON, Chicago.

A QUANTITATIVE APPROACH TO THE STUDY OF SPLENOMEGALY. ALVIN J. GORDAN, ERNEST C. HOLDER and SERGEI FEITELBERG, Arch. Path. **46**:320 (Oct.) 1948.

This papers deals with the description of a method to estimate quantitatively the percentages of white pulp, red pulp, and trabeculae, and with the attempts of the authors to draw some conclusions concerning the comparison of changes found in different types of splenomegaly. The authors use a method modified from that of Hwang and his associates to calculate the areas of their material. The microscopic field of the tissue is projected onto a piece of translucent paper fixed to a glass plate and the image is measured directly on the paper with a planimeter.

Spleens of 30 "normal" subjects and 71 spleens from patients with subacute bacterial endocarditis, Laennec's cirrhosis, leukemia, cardiac failure, polycythemia and Gaucher's disease were examined. The different components of the spleen were found to grow in different proportions in the various diseases. In Gaucher's disease the growth of the spleen was found to be predominantly in the red pulp, the trabeculae contributing only a little and the white pulp none at all to the enlargement. In cases of chronic portal hypertension there appeared to be a striking diminution in percentage of the white pulp, although the absolute weight remains the same. Thus it can be seen that the increase in size is due almost exclusively to red pulp growth, the white pulp remaining untouched by the process.

HAW CHAN, San Francisco.

TREATMENT OF NUTRITIONAL ANEMIA IN INFANTS. PHILLIP STURGEON, California Med. **76**:346 (May) 1952.

While iron deficiency is a common cause of anemia in infants, requiring specific treatment by administration of iron, there are other causes which require treatment equally specific. Anemia due to a nutritional deficiency can be improved only by providing the needed nutriment in sufficient quantity.

Two case reports are presented. One is of megaloblastic anemia in an infant, which was treated with a variety of vitamin preparations before administration of folic acid produced improvement. The other report is of anemia due to iron deficiency treated successfully with ferrous sulfate in a dosage 20 times that previously used prophylactically.

In prescribing an antianemic preparation the physician should assure himself that the dosage is adequate (for example, 0.5 gm. daily of ferrous sulfate for iron deficiency). "Broad-spectrum" preparations may be lacking in specific hematinics while containing a variety of vitamins which have no specific hematologic value.

PRYOR, Redwood City, Calif.

THE PICTURE OF CHRONIC GRANULOCYTOPENIA IN CHILDREN. MOJMIR R. VRTILEK, Helvet. paediat. acta **7**:207 (April) 1952.

Six cases of chronic granulocytopenia in children are reported. The patients were two boys and four girls in infancy and early childhood with recurrent febrile episodes of upper respiratory tract infection. Three children were allergic. Mild signs of constitutional physical retardation were evident in these patients. During the febrile episodes there was moderate lymphadenopathy and occasionally slight enlargement of the liver and spleen as well. At times allergic exanthemata appeared. The children displayed loss of appetite and failure to gain weight. Blood examinations revealed marked neutropenia with usually a shift to the left and toxic granulation. Because of an increase in absolute numbers of lymphocytes, in certain cases there was no leucopenia. In four cases there was a concomitant commensurate anemia, and in one severe thrombocytopenia. Monocytosis, persistence of the eosinophiles, and an increase in absolute numbers of lymphocytes appeared to be of favorable prognostic significance. In the bone marrow a moderate disturbance in maturation of the myeloid series was evident. In two cases phagocytosis of neutrophiles in the bone marrow was observed.

There is no specific treatment. Transfusions of whole blood and administration of antibiotics seem indicated. The disease picture extends over months and years; most commonly a spontaneous remission occurs. In only one case did panhematopenia develop, with a fatal outcome.

In the differential diagnosis leukemia, lymphoid reactions, and the remaining known granulocytopenias must be excluded. Pathogenetically, it appears likely that several factors are at work together and that allergic and toxic precipitating causes are reacting on a constitutionally weak bone marrow.

FROM THE AUTHOR'S SUMMARY.

INVESTIGATIONS CONCERNING CERTAIN DISEASES WITH HEMORRHAGIC DIATHESIS. S. VAN CREVELD, Schweiz. med. Wchnschr. **82**:399 (April 12) 1952.

Heparinized plasma shortened the coagulation time of hemophilic blood in vivo and in vitro more than citrate plasma and for a longer period of time. Furthermore, heparinized plasma increased prothrombin consumption during coagulation. Heparinized plasma preserved in the

cold or by drying maintains differences noted between transfusion of heparinized blood and that of citrate blood in the hemophilic patient. In all cases of hemophilia, the use of heparinized plasma offers great advantages over that of citrated plasma as introduction of treatment. Evidently in cases of severe anemia, plasma alone is not sufficient.

In another group of cases, an anticoagulant not related to heparin exists in the circulating blood. This anticoagulant is fixed probably to gamma globulin. Since it may be that this anticoagulant is an antibody to the antigen called antihemophilic factor, corticotropin was injected repeatedly, or cortisone was given repeatedly by mouth, with the result that the anticoagulant activity of the plasma was temporarily diminished. Attention is called to the diminution of the plasma accelerator globulin in cases of melena of the newborn, which may be the primary causative factor. The role of the platelets is discussed. Platelets furnish a factor (1) favoring the transformation of prothrombin to thrombin, and a factor (2) favoring the transformation of fibrinogen to fibrin. In human platelets a factor (3) was demonstrated which neutralizes added heparin. It is a phosphatide with thromboplastic properties. Suspensions of thrombocytes have been transfused in various pathological states accompanied by thrombopenia. It was possible to influence the thrombopenia and its consequences for several days.

AMBERG, Rochester, Minn.

A CASE OF SPORADIC CONSTITUTIONAL THROMBOPENIA. E. GRASSO, Minerva Pediatrica **4**:36 (Jan. 31) 1952.

A girl of 9 years had episodes of purpura, bleeding of the gums, and epistaxis. The bleeding time was prolonged; there was little or no retraction of a blood clot; the blood platelets were normal in number (200,000), but were large and did not tend to clump together. A blood marrow biopsy revealed many megakaryocytes, which were immature and tended to appear firm and compact in nature.

HIGGINS, Boston.

PAROXYSMAL TACHYCARDIA IN AN INFANT WITH SYNDROME OF SHORT P-R INTERVAL. HORACIO DE LA TORRE and ALBERTO DE CÓRDOVA, Rev. cubana pediat. **23**:226 (April) 1951.

A case of paroxysmal tachycardia in a 20-day-old infant is presented. Electrocardiography showed intraventricular nodal tachycardia at a rate of 300. The patient's arrhythmia responded rapidly to digitalis therapy. An electrocardiogram after return to normal rhythm showed the Wolff-Parkinson-White syndrome.

NELSON, San Francisco.

CONTRIBUTORS TO THE PROBLEM OF PYROGENIC REACTIONS FOLLOWING INTRAVENOUS INJECTION. KARL JOCHUM and ARMIN MAYER, Wien. klin. Wchnschr. **64**:375 (May 23) 1952.

Attention is called to possibility of growth of micro-organisms in minute faults of the glass of ampules. Rarely open channels were found where the ampules were sealed. Again, micro-organisms may lodge in these openings which may not be detected readily. Most pyrogenic reactions are caused by pyrogens in the instruments used for injection.

AMBERG, Rochester, Minn.

SPORADIC CASES OF HEMOPHILIA. H. ALTHOFF, Ztschr. Kinderh. **67**:343 (No. 3/4) 1949.

Two cases of hemophilia are described. No other cases in the family could be found. The author believes that the cause of hemophilia is a disturbance in the plasma thromboplastin and that similar, though milder, disturbances can be found in the plasma of the mother. The addition of plasma or plasma thromboplastin of the mothers reduced the coagulation time to a much less degree than the addition of plasma or plasma thromboplastin of healthy persons. The author thus considers these cases not truly sporadic and warns that absence of clinical cases of hemophilia in the family does not necessarily prove the occurrence of a true sporadic case.

GLASER, Jerusalem.

THROMBOSIS IN CHILDREN. MAIJA MIETTINEN, Acta pædiat. **39**:267 (No. 4-5) 1950.

A short description is given of various venous and arterial thromboses occurring in children. The frequency of sinus thromboses and occlusion of the abdominal aorta, their etiology, and the clinical pictures are discussed, and the literature on these conditions is surveyed. A report follows of a case of sinus thrombosis of the primary type in a 1-year-old and in a 10-month-old infant and also of a case of total thrombosis of the abdominal aorta in a newborn infant, the etiology of which was suspected to be umbilical sepsis, though this could not be proved.

FROM THE AUTHOR'S SUMMARY.

INVESTIGATIONS INTO HISTAMINE CONTENT OF UMBILICAL BLOOD. OSSI PETTAY, Acta pædiat. **39**:283 (No. 4-5) 1950.

The author has determined the histamine percentage of 25 specimens of umbilical blood plasma. Ten specimens of normal adult plasma served as control. On the average the histamine content of the umbilical plasma was found to be two to three times higher than that of the normal plasma. This difference is supposed to be due to lack of oxygen during birth.

FROM THE AUTHOR'S SUMMARY.

CHEST ELECTRODES FOR CHILDREN. ELIAS BENGTSSON, Acta pædiat. **39**:428 (No. 4-5) 1950.

The choice of electrodes for electroencephalographic chest leads in children is discussed, those in use for adults being inadvisable. An elastic band covering the entire thorax, by means of which electrodes of small diameter can be applied anywhere on the chest, is described.

FROM THE AUTHOR'S SUMMARY.

PLASMA TRANSFUSIONS IN HEMOPHILIA. S. VAN CREVELD and M. M. P. PAULSSEN, Nederl. tijdschr. verlosk. en gynaec. **95**:1818 (June 23) 1951.

With reference to differences found earlier between the effect of transfusion of heparinized plasma and of citrated plasma in patients with hemophilia, an investigation was made of the extent to which the effect on the coagulation time was preserved by using frozen and lyophil-dried heparinized plasma respectively. This freezing and lyophilic drying appeared to diminish the action of the heparinized plasma only slightly, the effect always being more favorable than that of the citrated plasma. From some clinical experiences reported here one may conclude that the use of heparinized plasma prepared according to the method recommended by the authors may have great advantages in hemophilic patients with hemorrhages, in any case as an introduction to treatment.

VAN CREVELD, Amsterdam, Netherlands.

A NEW METHOD TO JUDGE THE FUNCTION OF THE BLOOD PLATELETS IN DIFFERENT HEMORRHAGIC CONDITIONS BY MEANS OF HEPARIN. S. VAN CREVELD and M. M. P. PAULSSEN, Nederl. tijdschr. verlosk. en gynaec. **95**:1971 (July 7) 1951.

A number of patients with greatly varying hemorrhagic diathesis, accompanied by deficiency or dysfunction of the blood platelets, are discussed. In two of these patients the classification was difficult, even after extensive examination of clotting factors recently discovered. However, in both these patients the existence of a new functional anomaly of the blood platelets was demonstrated—this in contradistinction especially to the findings in two patients with hereditary thrombasthenia (Glanzmann); this anomaly consisted of a decreased capacity to neutralize added heparin. The possible significance of this phenomenon for the explanation of hemorrhagic diathesis is stressed.

The authors found this decreased capacity to neutralize heparin in a number of other patients also; in these cases, however, it was caused by a decrease in the number of thrombocytes.

Blood transfusion had a transitory, and to a certain degree favorable, influence on the disturbance in the neutralizing activity with regard to heparin.

The authors criticize the heparin-tolerance test in vitro as recommended by Waugh and Ruddick (1944) and used by many authors to establish a decreased or increased tendency toward coagulation. However, when oxalated plasma is used the amount of heparin which can be neutralized by this plasma will depend on the amount of platelets or products of platelets present.

VAN CREVELD, Amsterdam, Netherlands.

THE SERUM CONSTITUENTS ACTIVE IN THE THYMOL-TURBIDITY TEST. H. DEKEMA, Nederl. tijdschr. verlosk. en gynaec. **95**:3774 (Dec. 15) 1951.

The author found that beta globulin possesses an action which makes thymol turbid. The activity of thymol is caused by the phospholipids which are coupled with beta globulin. The most active component of these phospholipids was found to be lecithin. In diseases of the liver the thymol turbidity test probably indicates a phospholipoid disturbance and not a specific shift of the beta or gamma globulin in the protein spectrum.

VAN CREVELD, Amsterdam, Netherlands.

RESULTS OF THE TYING-OFF OF THE PATENT DUCTUS BOTALLI IN A NUMBER OF CHILDREN. F. H. ALBERS, Nederl. tijdschr. verlosk. en gynaec. **96**:131 (Jan. 19) 1952.

Among 16 children with patent ductus arteriosus several lacked one of the classic symptoms. In nine children heart catheterization was carried out before and after the ligation of the patent ductus. Before the operation, pressure in the right ventricle was always increased; two to five weeks after the operation, pressure had not yet dropped to the normal value in eight out of nine cases. After the operation the oxygen content of the venous blood was higher than before. In five patients a distinct murmur above the heart was still heard after operation; in one of these recanalization of the ductus was demonstrated.

VAN CREVELD, Amsterdam, Netherlands.

A NEW ELECTROCARDIOGRAPHIC SYMPTOM OF HYPERTROPHY OF THE LEFT VENTRICLE. J. B. KLEYN, Nederl. tijdschr. verlosk. en gynaec. **96**:378 (Feb. 16) 1952.

Because of theoretical considerations the author argues that lengthening of the R wave, measured between Q and S in Lead V_4 or V_5 of the electrocardiogram, may be an indication of hypertrophy of the left ventricle. The supposition was confirmed in the study of over 84 electrocardiograms in cases checked by autopsy.

VAN CREVELD, Amsterdam, Netherlands.

THE SIGNIFICANCE OF COPPER IN THE TREATMENT OF IRON-REFRACTORY HYPOCHROMIC ANEMIA. S. I. DE VRIES, Nederl. tijdschr. verlosk. en gynaec. **96**:611 (March 15) 1952.

A short survey is given of the literature on the influence of copper in the treatment of anemia in men and animals. The author, basing his opinion upon observations in eight patients, believes that hypochromic anemia, refractory against iron, and in which also the serum copper content is low, may be cured by administration of copper. It is supposed that the copper in such cases acts as a catalyzer.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat, and Ear

BRONCHOGRAPHY IN THE INFANT AND VERY YOUNG CHILD. FERNAND G. EEMAN, Ann. Otol. Rhin. & Laryng. **60**:793 (Sept.) 1951.

The history of bronchography is reviewed, going back to 1914 when Weingartner accidentally introduced bismuth into the tracheobronchial tree.

The following reasons for the unpopularity of the use of bronchography in children are presented and commented upon:

1. The risk of anesthesia: Utilization of tetracaine (pontocaine®) hydrochloride by fine spray or nebulization is advocated. Slow administration (20 to 30 minutes) and high dilution of the agent employed are stressed. Eeman finds proof lacking of increased sensitivity of children to topical anesthetic drugs as compared to adults. Very young children and infants may have satisfactory examinations without anesthesia.

2. The risk of the technical procedure of the introduction of the opaque oil: Use of a soft catheter, introduced transorally or transnasally, obviates the necessity for bronchoscopy except in a few cases. [I believe that, if bronchography is indicated, so also is preliminary bronchoscopy.]

3. The risk of respiratory trouble due to the filling of the tracheobronchial tree: The smaller capacity of the infant tracheobronchial tree should be remembered, for overfilling is as dangerous in infants as in adults. Fluoroscopic control is of value.

4. The risk of intoxication due to the iodine: This risk may be avoided by observing precautions in known cases of acute tuberculosis; by using iodine skin tests two days prior to bronchography; by not exceeding the necessary amount of radiopaque oil; by utilizing topical rather than general anesthesia, and by aspirating the iodized oil immediately following bronchography or instituting postural drainage.

STEELE, Kansas City, Kan. [A. M. A. ARCH. OTOLARYNG.].

MENINGOCOCCIC INFECTION OF THE EAR. R. POCH VINALS, Arch. pediat. **2**:91 (July) 1951.

Full case histories of 11 children with lesions of the ear secondary to meningococcic meningitis are given. The author believes that the various involvements of the inner ear, the middle ear, and the labyrinth are often overlooked in cases of acute meningitis. His study is more concerned with diagnostic points than with treatment.

The chain of events leading to an ear infection are (1) rhinopharyngitis or trauma; (2) septicemia; (3) meningitis, and (4) ear involvement.

Because of the acute illness of meningitis, deafness may not be noticed until later.

Frequently, also, there are organisms present other than the Meningococcus, and in each case presented there were different infectious and traumatic factors, but in all cases there were ear involvements not at first noticed.

ALLEN, San Francisco.

THE PROBLEM OF ADENOID SURGERY IN CHILDREN UNDER TWO. S. S. SAMUELS, Eye, Ear, Nose & Throat Month. **31**:85 (Feb.) 1952.

The question of the surgical removal of adenoids and tonsils, or of the adenoids alone, in very young children has been the subject of an infinite amount of discussion among physicians for many years. Samuels considers the adenoids to be much more important in the production of abnormal conditions than the tonsils. The adenoids are hidden from view and are therefore often overlooked. The tonsils, however, are plainly to be seen, and therefore pathologic processes in them are readily diagnosed.

If the adenoids are quite large, or the nasopharynx unusually small, so that the adenoids become relatively large, they may be the cause of obstruction to adjacent structures, owing to their natural position. In an epipharynx small from the front backward the adenoid easily obstructs the posterior nasal choanae, especially in the infant or very young child. The resultant obstruction to the respiratory channel is evidenced by mouth-breathing, continually running nose, snoring, and difficulty in feeding because the child is unable to swallow while the mouth is open to breathe. Obstruction takes place when relatively enlarged adenoid tissue blocks the orifices of one or both Eustachian tubes. In the very young child this is evidenced by the repeated occurrence of otitis media accompanying many, if not all, upper respiratory infections. Later in life this obstruction is manifested by the onset of so-called catarrhal deafness.

Besides the damage obstruction can possibly cause, the adenoids may cause difficulties of an infectious nature. They are subject to attack by many and varied pathogenic organisms. Acute upper respiratory infections may invade the adenoid tissue, and, while some feel that the adenoids are part of the immunologic resources of the body, they show little ability to rid themselves of infection and often become chronically diseased. In this state they contribute to the postnasal drip with its disturbing cough and the infection of the ears and adjacent sinuses. Also, the adenoids by their intrinsic infection may be the focus of a bacterial allergy.

Age is no contraindication to the removal of adenoids. Ether anesthesia, as light as practicable, is used routinely. On most children, except those under 6 to 9 months of age, a routine tonsillectomy is done, since this takes only a short time and may obviate the need for a later

operation. The adenoids are then completely and painstakingly removed by means of an adenotome, curette, and punch, the latter under direct vision. Besides preventing regrowth of tissue, the complete and thorough operation will generally avert postoperative hemorrhage. The latter in most cases occurs from tags of unseparated tissue and their remaining blood supply.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

HOARSENESS IN INFANTS AND CHILDREN. P. H. HOLINGER, K. C. JOHNSTON, and R. J. MCMAHON, Eye, Ear, Nose & Throat Month. **31**:247 (May) 1952.

Hoarseness in infants and children is a symptom requiring as careful and complete a study as in the adult. Neck and chest x-rays, a neurological examination, and, finally, a direct examination of the larynx of the infant are necessary to establish the diagnosis of hoarseness in the infant.

Among the various causes of hoarseness in the newborn child, both congenital anomalies and birth injuries must be considered as well as the stridulous crowing noise designated as congenital laryngeal stridor.

In children of preschool and school age the commonest cause of acute hoarseness is the acute laryngeal manifestations of respiratory tract infection. However, injuries may also result in acute hoarseness from local edema or hematoma. Chronic hoarseness may be caused by vocal abuse, chronic respiratory tract infection, or laryngeal papillomata. Careful examination of the entire patient, with chest x-rays, blood and urine examinations, and a thorough examination of the full length of both cords by mirror or direct laryngoscopy, is necessary to establish a diagnosis. In the chronic conditions voice correction therapy is of great value. In papilloma of the larynx endoscopic removal is the procedure of choice.

In the school-age child the problem of hoarseness, like the hearing problem, needs the complete understanding of both the parents and the teachers. Early recognition and careful management may avert permanent vocal cord damage.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

SEROLOGIC INVESTIGATIONS ON THE EDEMA FLUID FROM NASAL POLYPS: A PRELIMINARY REPORT. FETER BERDAL, J. Allergy **23**:11 (Jan.) 1952.

Specific antibodies were present in greater concentration in fluid squeezed from nasal polyps than were present in the blood serum or in the fluid obtained from a cantharidin bulla produced on the skin. Dilutions of these fluids were injected intracutaneously into the back. The site of the injections were tested 24 to 48 hours later with allergens to which the individual was known to be sensitive.

HOYER, Cincinnati.

ELECTROCOAGULATION OF TONSILS. F. L. WAHRER, J. Internat. Coll. Surgeons **17**:224 (Feb.) 1952.

Wahrer has used electrocoagulation of the tonsils for the past 25 years and continued to use it. There are a few indications for this type of therapy, but it is not a good method for routine tonsillectomy.

A bipolar electrode, slightly curved and about 3/8 in. (1 cm.) long, is used, and the needles are inserted into the tissue slightly less than 1/4 in. (0.6 cm.). Only enough current is used to achieve the complete dehydration of the area of tonsil that is being coagulated, and three widely separated areas are chosen for coagulation at each sitting.

For anesthesia purposes 10% cocaine is applied topically, three applications at five-minute intervals. The tonsil tissue is watched. The instant there is blanching, the current is turned off. The current should never be left on until the tissues become white or begin to swell.

The removal of the average pair of tonsils takes from five to six treatments for each tonsil and is spread over a period of about 10 to 12 weeks. One tonsil is treated at one sitting, and the other tonsil is treated one week later.

GORDON, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

RHINOLOGY IN CHILDREN: RÉSUMÉ OF AND COMMENTS ON THE LITERATURE FOR 1950. D. E. S. WISHART and J. B. WHALEY, Laryngoscope **61**:957 (Oct.) 1951.

This is the usual fine review of otolaryngology in children. Most important subjects are well covered.

There still is no cure for the common cold. Antihistamines may lessen the early symptoms only, but the course of the cold is unaltered. Some serious side-effects have been noted. The value of constrictors in the treatment of colds is being questioned by more and more authorities.

It is felt that there is an optimum concentration of penicillin, over or under which its value decreases. Streptomycin soon loses its effect because the bacteria quickly become insensitive to it. They do not, however, become insensitive to aureomycin or chloramphenicol. The former is better for Gram-positive and the latter for Gram-negative bacteria.

Questions concerning sinusitis, the tonsils, allergy, and the use of the nasopharyngeal radium applicator are discussed. Most authorities feel that the standard Crowe applicator, if used properly, is without harm and does much good in selected cases. Several good articles on new growths are reviewed. It is believed that with proper treatment (electrocoagulation and interstitial irradiation) almost all nasopharyngeal fibromas can be nearly or entirely eradicated. This should be done transorally and often is possible at operation.

HITSCHLER, Philadelphia [A. M. A. Arch. Otolaryng.].

THE PROBLEM OF THE PRESCHOOL DEAF CHILD. JOHN E. BORDLEY, Laryngoscope **62**:514 (May) 1952.

In order to determine the extent, cause, and kind of hearing loss in the preschool child, there must be the proper equipment and also sufficient cooperation from the parents. During any hearing-speech training program the doctor should be in continual touch with the patient in the role of counselor.

Diagnosis is difficult. A most careful history is necessary. A printed questionnaire (shown) is helpful. Examination must include that of the nose, pharynx, and Eustachian orifices, as well as of the ears and hearing. General performance tests aid in determining the child's mental state. The hearing itself is tested by the tuning forks, by monitored sound effects in a sound-proof room, and by the audiometer. The latter includes both the pyschogalvanic skin-resistance audiometer and the pure-tone subjective audiometer (when possible).

An analysis of the etiologic factors involved in 485 cases is given. Two causes are emphasized: mothers receiving immune globulin during the first trimester of their pregnancy and cyanosis at birth.

Early diagnosis, with an intelligent training program using amplification, is most important and may mean the difference between a normal and an abnormal upbringing.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

FURTHER OBSERVATIONS UPON THE DIAGNOSIS OF DEAFNESS IN YOUNG CHILDREN. M. R. DIX and C. S. HALLPIKE, Brit. M. J. **1**:235 (Feb. 2) 1952.

Dix and Hallpike present still another confirmation of the fact first observed by Urbantschitsch many years ago that nearly all profoundly deaf children have some remnant of hearing which may be used in auricular training for language and speech. These children must be trained in a conditioned response in order to make quantitative hearing tests. The authors use a refinement of the Ewing technique which has already gone through a number of steps in its evolution. The apparatus uses interesting pictures to attract the child's attention. The association with sound is developed, for the child is induced on hearing the sound to press a button which turns on a light illuminating the picture. The sound or sounds are the frequencies of an audiometer and can be controlled as to loudness so as to obtain threshold of pitch hearing. Thus, an audiogram can be obtained.

[The principle is the same as that used by Wishart (Toronto) in his method and is analogous to the recently invented Jack-in-the-box technique. Still other methods are the use of an associated tactile stimulus (Macfarlan) and the galvanic skin response to a small electric shock.]

The authors take great pains to detail the importance of the "set" of the test in order to get concentration and to avoid distraction. In every way the article covers all the items that a novice should know and follow.

In addition to the test itself, there is valuable exposition of the conclusions to be drawn from the findings, particularly in relation to the educational program and the implications as to the psychology of these children.

[It seems unusual to find in this article a statement that "no great difficulties have been encountered in assessing the mental capacities," an observation not before recorded by those most familiar with the deaf child. Aphasias, though rare, are not mentioned as in conflict with conditioned-response testing, nor is profound attention deafness mentioned. Behavior problems and altered psychology, particularly of the "blocking" type, are so commonly the result of childhood deafness that they present a psychological overlay that is often inseparable from mental inferiority. It is strange that these stumbling blocks in the testing of the young deaf child without language are not mentioned.

The same issue of the *British Medical Journal* recognizes the excellence of the article and the importance of its subject in an editorial.]

DOUGLAS MACFARLAN, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

SURGICAL CORRECTION OF CONGENITAL MALFORMATIONS OF THE AURICLE WITH ATRESIA OF THE EXTERNAL AUDITORY CANAL: REPORT ON THIRTY-THREE CASES. MARCEL OMBREDANNE, Ann. oto-laryng. **68**:5, 1951.

The author reports 33 cases of congenital malformation of the auricle with complete atresia of the auditory canal, occurring mainly in children from 7 years of age and upward but also in a few adults.

The technique followed consisted mainly in the reconstruction of the malformed auricle by plastic surgery, with the use of cartilaginous grafts or acrylic implants. Then an auditory canal was shaped, the external extremity of which was placed in the center of the newly formed auricle and the walls of which were lined with epithelium from a full-thickness graft and a pedunculated flap. The inner extremity of this canal was placed over the previously fenestrated external semicircular canal.

This procedure has proved to be very difficult, but has been encouraging in that 22 good results and 8 mediocre results from a functional point of view have been obtained. In seven of the cases of complete aplasia and complete absence of the middle ear and ossicles encouraging results were obtained.

VIOLÉ, Los Angeles [A. M. A. Arch. Otolaryng.]

LYMPHOBLASTIC SARCOMA OF THE INFERIOR TURBINATE. MARCEL GIGNOUX and JEAN GAILLARD, Ann. oto-laryng. **68**:176 (Feb.-March) 1951.

Two cases of lymphoblastic sarcoma of the nasal fossae located on the inferior turbinate in boys of 8 and 11 years of age are reported. Early diagnosis was possible in each case, the diagnosis depending upon the anatomicopathological examination. The sensivity of these tumors to physical agents contraindicated dangerous surgical procedures. Transcutaneous irradiation must be performed by radium puncture of the primary lesion. X-ray therapy of the surrounding glandular structures must be performed. By physical therapy alone Gignoux and Gaillard obtained a 12-year cure in one case and an apparent cure of several months in their second case.

VIOLÉ, Los Angeles [A. M. A. Arch. Otolaryng.].

THE ARTERIAL TENSION IN THE COURSE OF TONSILLECTOMY UNDER LOCAL ANESTHESIA. J. P. DEREYNIER, Practica oto-rhino-laryng. **12**:333, 1951.

DeReynier performed a tonsillectomy on a young woman, using a local anesthetic of 1% procaine hydrochloride with epinephrine. There were no immediate after-effects, but one-half hour after the completion of the operation the patient suffered a complete collapse, became unconscious, and was in a true state of shock. Under proper stimulation she made a recovery in about two hours.

Being impressed by this episode and recalling the work of Escher on fluctuations in arterial tension as a late aftermath of tonsillectomy, the author made detailed observations on the blood pressure both before and after operation in 33 patients who had undergone tonsillectomy with local anesthesia. Ten of his patients showed a slight elevation, of 20 to 40 mm. Hg, after the

anesthesia; 10 other patients evidenced marked hypertension, while in 13 there was a slight drop in the tension immediately after the actual surgery. However, beginning with the first half-hour after the completion of the surgery there was a decided drop in the tension. In 22 cases the tension fell from 5 to 50 mm. Hg below the normal. In these cases the author feels that the delayed reactions of the patient are due not to the procaine but, rather, to the epinephrine. This is particularly noticeable in emotional and anxious patients or in those who have a neurovegetative dystonia, those with very labile arterial tension, and, particularly, those who have a tendency toward hypotension. He suggests that all local surgery should be done in a well-established hospital, that an evaluation of the patient be made, and that if the patient seems to fall into any of the above-mentioned groups, the surgeon be prepared for any possible late reactions. Proper preoperative medication should be instituted, epinephrine eliminated from the solution if possible, or, better still, the operation performed with the patient under general anesthesia.

PERSKY. Philadelphia [A. M. A. Arch. Otolaryng.].

PUNCTURE OF THE MASTOID ANTRUM IN INFANTS. PLUTARCO TORRES LUQUIN, An. Soc. mex. oto-rino-laring. **3**:79 (July-Sept.) 1951.

The author advocates the puncture of the mastoid antrum in infants who present manifest otitic complications, severe gastrointestinal disturbance, undetermined infectious syndrome, and in cases of cerebral meningitis to establish a diagnosis of a possible mastoiditis. He has a specially constructed double needle which can be used for both diagnostic and therapeutic purposes. When it is used for diagnosis, aspiration of the secretion in the mastoid antrum is done, and microscopic, cytologic, and bacterial studies are made. At other times the antrum may be irrigated with either isotonic sodium chloride solution or solutions containing antibiotics. This procedure can also act as a guide in determining the indications for a more extensive antrotomy. Luquin believes that when the antral puncture presents evidences of an infection, antrotomy should be done as quickly as possible. On the other hand, when the exploration shows a healthy antrum with good permeability, an antrotomy is a contraindication. He further describes the particular type of needle in the performance of this antrum puncture.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

CONSIDERATION OF A THOUSAND CASES OF TONSILLECTOMIES IN CHILDREN UNDER ETHYL CHLORIDE ANESTHESIA. MARIO RIUS, An. oto-rino-laring. Uruguay **21**:73, 1951.

Rius believes that ethyl chloride should be the anesthetic of choice for tonsillectomy and adenoidectomy in children. It is easy to use and pleasant for induction. It eliminates a considerable amount of psychic trauma. It does not depress respiration, its elimination is very rapid, and recuperation from the anesthetic follows quickly. Caution is necessary in supplemental use of barbiturates, since it is difficult to evaluate proper dosage, and they may cause laryngeal spasm, depress respiration, and have a variable reflex action depending on a psychic state of the patient. Rius further believes that intubation is unnecessary, since this is a very short operation, and that there are increased dangers with its use. Furthermore, recuperation is prolonged and very often accompanied by untoward complications when intubation is used.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

BIOLOGY AND PATHOLOGY OF TONSILS. W. ROTHMUND, Deutsche med. Wchnschr. **75**:384 (March 24) 1950.

The tonsils are considered as purely lymphatic organs, modified lymph nodes of the mucous membrane. They are assumed to serve the posterior nose and throat regions as filter organs. It is emphasized that their infection, including tuberculous infection, does not take place by way of the crypts.

AMBERG, Rochester, Minn.

ETIOLOGY OF DEAFNESS IN YOUNG CHILDREN. JOHN E. BORDLEY and WILLIAM G. HARDY, Acta oto-laryng. **40**:72 (Jan.) 1951.

Using the galvanic skin response, the authors were able to test the hearing in quite young children and in many instances to establish diagnosis. They felt that for one-third of the group

of 296 children a satisfactory diagnosis could not be made. In other instances there was difficulty of choice among several etiologic factors. Eighty-eight of the group had been exposed to the causative factor of their deafness by the time delivery was completed. Thus, from a point of view of prevention of birth injuries and erythroblastosis many of these instances of deafness might have been avoided; over half of the children should have started life with normal hearing. Add to this the group which had meningitis, measles, and middle ear disease, and the number of fairly preventable hearing losses becomes larger. One material help may be immunization for rubella before pregnancy.

LEWY, Chicago [A. M. A. Arch. Otolaryng.].

UNDIAGNOSED OTITIS MEDIA. G. A. HOOGLAND, Nederl. tijdschr. verlosk. en gynaec. **95**:3477 (Nov. 24) 1951.

Eleven cases of acute otitis media are described which occurred in the course of infectious diseases which had not been diagnosed before admission to the hospital. In young children, otitis media frequently takes an atypical course. Only inspection of the tympanic membrane makes it possible to make an exact diagnosis and to administer adequate therapy.

VAN CREVELD, Amsterdam, Netherlands.

ABSCESS FOCUS IN PERITONSILLAR ABSCESS. R. TAKAHASHI, Japanese J. Otolaryng. **23**:453-455 (Nov.) 1951.

Tonsillectomies were performed during the acute stage of quinsy. The tonsils were then examined, both macroscopically and microscopically. Takahashi states that in the majority of instances tonsillar tissues are partly involved in the abscess but the walls of this focus are composed for the most part of infiltrated capsular tissues.

In some instances the location of the abscess was what he terms intracapsular, and at times the abscess extended to an extracapsular structure.

Takahashi does not agree with the observation that the abscess is wholly extracapsular in origin or with that which holds that the abscess is limited to intracapsular and intertonsillar extent.

HARA, Los Angeles [A. M. A. Arch. Otolaryng.].

Diseases of Lungs, Pleura, and Mediastinum

VITAL CAPACITY AND MAXIMUM BREATHING CAPACITY OF ADOLESCENT BOYS. R. E. MOORE, Great Ormond Street J. **2**:137 (Dec.) 1951.

Studies of the vital capacities and maximum breathing capacities of 152 average adolescent boys were made. Formulas for calculating these values were developed, and it was shown that there was a high degree of correlation between the two values. Maximal breathing capacity may be predicted from vital capacity.

MCGUIGAN, Evanston, Ill.

THE PATHOGENESIS OF CHYLOTHORAX IN THE CHILD. G. CADEDDU, Ann. ital. pediat. **5**:1 (Feb.) 1952.

The author describes a case of chylothorax in a child affected by tubercular polyserositis caused by mediastinic adenopathy and confirms the importance of roentgen therapy.

FROM THE AUTHOR'S SUMMARY.

PRELIMINARY NOTE REGARDING INTERSTITIAL EMPHYSEMAS COMPLICATING ACUTE PULMONARY PROCESSES IN EARLY INFANCY. B. TARACENA DEL PINAL and M. DOMINGUEZ RECIO, Acta pediat. españ. **10**:70 (Jan.) 1952.

In 60 cases studied, 14 infants were found at autopsy to have interstitial emphysema complicating acute pneumonic infections. All patients were poorly nourished infants under 3 months of age. The mechanism causing this lesion is believed to be as follows: The infectious process weakens the walls of the alveoli; the inflammation of the bronchioles with the accumulation of secretion in these acts in some cases as a valve which makes the force of inspiration

stronger than expiration, and with each inspiration some air is forced into the alveoli with already weakened walls; the alveolus finally is perforated and emphysema results.

The diagnosis is obvious when the emphysema invades the tissues of the neck, but may be made roentgenologically. Cuts are included. The possibility of a therapeutic pneumothorax on the affected side should be considered.

ALLEN, San Francisco.

SPONTANEOUS PNEUMOTHORAX IN THE INFANT. GLADYS SUDZUKI HILLS, Rev. chilena pediat. **23**:115 (March) 1952.

The authors report three cases of pneumothorax in infants aged 7, 24, and 15 months, the pneumothorax in one case caused by a rupture of a tuberculous cavity and in the other two cases following pneumonia. The seriousness of the tuberculous pneumothorax was contrasted with the benignity of the other two cases. In the benign type there were no changes in the blood sedimentation rate or in the blood count. The authors favor using a permanent drainage that helps in the reabsorption of the pneumothorax, thus diminishing the hospitalization time.

FROM THE AUTHOR'S SUMMARY.

ON UNIVERSAL REACTIONS IN CONNECTION WITH TREATMENT OF ASTHMATIC CHILDREN WITH BACTERIAL VACCINES. E. WINGE FLENSBORG, Acta pædiat. **39**:192 (No. 3) 1950.

One hundred sixty-two asthmatic children were treated with vaccine of ordinary pathogenic bacteria from the upper respiratory tract; 63 universal reactions were observed in 42 patients (26%); 24 patients (15%) reacted to the first dose, while 33 (20%) had one or more reactions later in the course of the treatment. Highest frequency of reactions was during the first four years of life.

The reactions may be classified as slight (catarrhal affection and/or subfebrile temperature), medium severe (asthmatic wheezing with or without subfebrile temperature and catarrhal condition), and severe (attacks of asthma and/or high temperature). Severe forms were more frequent in later reactions than in the first one.

The time of onset of the reactions averaged 48 hours after the injection.

Repeated overdosage without regard even to slight reactions may produce status asthmaticus or a persistent rise of temperature.

A fatal case is reported in which death was presumably caused by an injection of vaccine containing only 2,600 bacteria in a 1-year-old patient who previously displayed only a very slight reaction to the same dose. This case and others (which were not fatal) illustrate that the sensitiveness of the patients to the bacterial vaccine may vary widely and indicate the importance of close supervision and very cautious dosage of bacterial vaccines for patients suffering from asthma.

The reactions after "genuine" allergen extracts may vary far more than after bacterial vaccines. The former are, furthermore, frequently immediate reactions; the latter, late ones.

The universal reactions of asthmatic nature which frequently follow even small doses of bacterial vaccine support the assumption of the presence in such children of an allergy to bacteria, to the decomposition products of the bacteria, or to substances produced by the organism's defensive measures against the bacteria.

FROM THE AUTHOR'S SUMMARY.

SIGNIFICANCE OF THE TEST EXCISION ACCORDING TO DANIELS FOR DIAGNOSIS AND FOR JUDGING THE OPERABILITY OF PATHOLOGIC PROCESSES IN LUNGS AND MEDIASTINUM. G. BOSMAN, N. G. M. ORIE and H. N. HARDERS, Nederl. tijdschr. verlosk. en gynaec. **95**:3382 (Nov. 17) 1951.

The technique of the test excision of the deep-lying supraclavicular lymph nodes as described by Daniels (1949) was applied to 100 patients. On finding a tuberculous lymph node, one should take into account that there need not exist any connection between this finding and the process to be examined.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

MANAGEMENT OF INTUSSUSCEPTION IN INFANTS AND CHILDREN. T. C. MOORE, Ann. Surg. **135**:184 (Feb.) 1952.

The literature concerning intussusception in infants and children is briefly reviewed.

Forty-three cases of intussusception are reported. To illustrate certain differences between intussusception in infants and in children, the patients have been divided into two groups: infants under 2 years of age and children over 2 years of age.

The clinical histories for infants were remarkably uniform. Most of the patients were healthy, well-nourished infants who had suffered sudden onset of intermittent colicky abdominal pain and vomiting with the subsequent passage of bloody stools, which when mixed with mucus occasionally had a "currant-jelly" appearance. In those cases in which early treatment was not given, the picture was that of progressive strangulated obstruction of the small intestine, resulting in death. The most revealing physical findings were limited to the abdomen and rectum. The presence of a mass was established by rectal or by abdominal examination in 84% of cases.

In children the onset of symptoms was more prolonged and less dramatic than was generally experienced in infants. Thus, the likelihood of mistaken or delayed diagnosis is considerably greater in the case of the older patients.

The experience with attempted nonoperative reduction in 17 cases is discussed, and the limitations of the method are cited.

The speed with which the intussusception is recognized and effectively treated is unquestionably the most important factor influencing the outcome.

BANTIN, Omaha.

INTUSSUSCEPTION OF THE APPENDIX WITH COMPLETE INVERSION OF THE APPENDIX AND PROTRUSION FROM THE ANUS. D. DUNAVANT and H. WILSON, Ann. Surg. **135**:287 (Feb.) 1952.

Intussusception and inversion of the appendix with protrusion of the cecum and appendix through the anus are uncommon.

The authors report in detail such an occurrence in an 8-month-old boy. They present a new and satisfactory operative procedure useful in the management of such a problem.

BANTIN, Omaha.

HIRSCHSPRUNG'S DISEASE AND CONGENITAL MEGACOLON. E. ELIZABETH LEON and ROLLA G. KARSHNER, California Med. **76**:276 (April) 1952.

Hirschsprung's disease and congenital megacolon are recognized as separate entities. They differ one from another in clinical, roentgenographic, and histologic features.

Conservative treatment of patients with Hirschsprung's disease is ineffective; surgical therapy with a new technique is beneficial. In congenital megacolon, operation is futile and may be harmful, whereas patients may be benefited by conservative measures and improvement may occur spontaneously after adolescence.

PRYOR, Redwood City, Calif.

THE CELIAC SYNDROME. J. A. BIGLER, Illinois M. J. **101**:21 (Jan.) 1952.

At the Children's Memorial Hospital, Chicago, during the past six years the following conditions have been observed: cystic fibrosis of the pancreas, 50 cases; celiac disease, 9 cases; steatorrhea, 5 cases, and carbohydrate intolerance, 5 cases. This report is made from the material of these cases. The histories, symptoms, physical and laboratory findings, differential diagnosis, prognosis, and therapy in the cases are discussed.

BARBOUR, Peoria, Ill.

EFFECT OF ACTH, CORTISONE AND PROGESTERONE ON PATIENTS WITH CHRONIC HEPATIC DISEASE. W. P. HAVENS JR.; R. M. MYERSON, and I. N. CARROLL, Metabolism **1**:172 (March) 1952.

Fifteen patients with hepatic cirrhosis and three in the convalescent phase of viral hepatitis were treated with cortisone (50 to 100 mg. intramuscularly, daily for 8 to 165 days), corticotropin

(20 to 25 mg. subcutaneously every six hours for 10 to 27 days) or progesterone (100 mg. daily intramuscularly for 24 to 30 days). Apart from the frequent observation of an improvement in sense of well-being it was impossible to distinguish the improvement which occurred from that which might have resulted from the regimen of diet and rest which these patients received. Increase in retention of fluid, psychosis, altered glucose-tolerance tests, coma and death were associated with the courses of therapy, if not ascribable to them, and these hazards outweighed the benefits of the use of these therapeutic agents.

KAPLAN, Cincinnati.

REPORT ON THE WORK OF THE GASTRO-ENTERITIS UNIT AT THE HOSPITAL FOR SICK CHILDREN FOR THE YEAR 1950. J. L. GREAVES and A. S. WELCH, Great Ormond St. J. **2**:115 (Dec.) 1951.

One hundred and thirty-nine patients with diarrhea and vomiting were admitted to the hospital during 1950. Of these, three-fifths showed evidence of associated parenteral infection, the greater number of these being in the older age groups. Infection was usually in the upper respiratory tract, most commonly in the ears. Mortality was 4.3%. In 121 cases intravenous infusions were required, and in 25.5% of these phlebitis developed.

McGUIGAN, Evanston, Ill.

INGUINO-SCROTAL SWELLINGS OF CHILDHOOD. A. E. DE SA, Indian J. Child Health **1**:1 (Jan.) 1952.

The author describes various conditions occurring in children which are due to failure of the processus vaginalis to seal off. Hydrocele and hernias are common, and failure to explore the entire processus vaginalis may result in the need for later surgery.

McGUIGAN, Evanston, Ill.

EPIDEMICS OF ENTERITIS IN INFANTS PRODUCED BY PATHOGENIC STRAINS OF COLI BACTERIA. H. OPITZ, Helvet. paediat. acta **7**:1 (March) 1952.

Two epidemics of enteritis are reported which seemed principally localized in hospital wards. The causative agent in both instances was Bacillus coli strains, O 111/B4 and O 55/B5.

Both epidemics appeared during the cold season, and young infants were mainly affected. In cases of diarrhea among infants over six months of age, neither strain of coli was isolated except rarely, and among children more than one year old they were never found.

In about 10% of the infants, healthy carriers were found, but never among the nurses and attendants. The clinical picture was not fundamentally different from that of the ordinary dyspepsias.

Streptomycin and sulfonamides failed, but the effect with aureomycin and chloramphenicol was prompt.

During times when there were no epidemics, both pathogenic groups of bacilli coli were found only temporarily among dyspeptic diseases of infants, and even during the epidemics they were never found among dyspeptic infants of other wards.

The determination of the agglutination titer showed few useful results.

The infectivity was very high. Epidemiological considerations were reviewed. Adults seem generally nonsusceptible, as self-experiments have shown.

The part played by these pathogenic strains of coli in dyspepsias of infants and their relations to Esch. coli are discussed.

FROM THE AUTHOR'S SUMMARY.

A TEST FOR TRYPSIN IN THE STOOLS. G. DE MURALT, Helvet. paediat. acta **7**:70 (March) 1952.

The author describes a modification of Shwachman's original gelatin-film-test technique. Through the use of higher fecal dilutions (1:50 and 1:100) instead of the usual 1:5 and 1:10 dilutions and a 5% solution of sodium bicarbonate to prepare the dilutions, a certain number of causes of error may be avoided.

By means of the test, the stools of 21 patients with celiac disease, 23 patients with pancreatic fibrosis, and 70 control patients with diseases other than pancreatic fibrosis and celiac disease were studied.

In all cases of celiac disease, the diagnosis was confirmed by duodenal drainage. In 14 cases of pancreatic fibrosis, the diagnosis could be confirmed by one or more duodenal intubations. Seven patients died; in all of these the pathology was typical of pancreatic fibrosis with bronchiectasis.

In infants and small children, a negative film test (no liquefaction of the gelatin layer of the film, even at a dilution of 1:5) is an evidence of deficient pancreatic trypsin secretion, nearly always due to pancreatic fibrosis.

A positive film test (liquefaction of the gelatin layer of the film up to a dilution of 1:100) is evidence against a deficient pancreatic trypsin secretion but does not always exclude pancreatic fibrosis. Certain incomplete forms of pancreatic fibrosis have a highly diminished secretion of lipase and diastase but a fairly normal secretion of trypsin. They may show a positive film test.

False positive film tests may be due to such causes of error as presence of urine or bacterial gelatinase in the stools or administration of penicillin or pancreatic ferments.

The method allows the dosage of the pancreatic ferment preparations necessary to overcome the diminished or abolished pancreatic trypsin secretion.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL ATRESIA OF THE ESOPHAGUS. DINA LAZZARO-BENINCASA and E. CAFFARATTI, Minerva pediat. **4**:47 (Jan. 31) 1952.

A case of congenital atresia of the esophagus is described, in which there was no esophageal-tracheal communication. No gas was found by x-ray in the stomach or intestines. Permission for operation was refused. Postmortem examination confirmed the diagnosis.

HIGGINS, Boston.

INFECTIOUS HEPATITIS IN CHILDREN. M. SAGGESE, Pediatria **60**:51 (Jan.) 1952.

An epidemic of infectious jaundice, occurring in a hospital in Naples, involved 16 of the 80 children in the various wards. The children were between 11 months and 3½ years of age. There were two deaths, both in undernourished rachitic children. No prodromata were noted. Fever persisted for only a few days, but symptoms lasted for about two weeks. Jaundice, acholic stools, enlarged liver, and spleen were present. The epidemic apparently was not over at the time the paper was written. The cases were not limited to any one ward, but were scattered throughout the hospital. No definite solution of the epidemiology of these cases had been established.

HIGGINS, Boston.

STREPTOMYCIN IN THE TREATMENT OF BACTERIAL DIARRHEAS IN INFANCY. ANTONIO PEREZ FERNANDEZ, Acta pediat. españ. **10**:64 (Jan.) 1952.

Streptomycin has proved effective in a large number of cases of bacterial diarrhea when due to both Gram-negative and Gram-positive bacteria. The sulfonamides are cheaper and very effective in many cases, but streptomycin by mouth has been very useful after the failure of sulfonamides and other methods. Two such cases are reported in detail. Penicillin and streptomycin together may be even more effective in certain cases.

According to the author, he has had no deleterious effects in the use of this antibiotic in infantile diarrhea.

ALLEN, San Francisco.

A CASE OF "FLOATING LIVER." JAIME DEAN GUELBENZER, Acta pediat. españ. **10**:80 (Jan.) 1952.

The rarity of "floating liver" prompted the author to publish this report. The patient was a newborn infant, without any significant past history prenatally or during delivery. Except for a slight edema of the hands, the child appeared normal. However, on palpation of the rather flaccid abdomen, a mass the size of an orange, but with an irregular ovoid shape, was palpated.

It was freely movable to the right or left and could be depressed below the level of the umbilicus. The percussion note over the entire upper right abdominal quadrant was flat rather than tympanitic.

An x-ray with barium showed a loop of colon in the usual position of the liver and the liver displaced downward and medially. It would seem to be due to weakness of ligaments, but unfortunately further study and autopsy following the child's death, within a few days after the first x-ray, were impossible because of the noncooperation of the family.

Another reason for reporting this case is that it would seem that the case throws some doubt on former theories of causation such as trauma, falls, or scoliosis.

ALLEN, San Francisco.

COMPARISON OF THE BACTERICIDAL ACTION OF THE JUICE OF STOMACH AND DUODENUM AGAINST BACILLUS COLI IN INFANTS WITH AND WITHOUT INTESTINAL DISEASE. O. BRAUN and A. LEHNERT, Ztschr. Kinderh. **68**:57 (No. 1) 1950.

The bactericidal action of the stomach and duodenal juice against Escherichia coli was tested by culture methods in children in whose gastric and duodenal juice Esch. coli had not been found. The bactericidal action was always found to be stronger in the stomach than in the duodenum; the authors believe that the function of the duodenum is dependent upon the amount of stomach juice present in the duodenum and upon the function of the gastric juice. The bactericidal action was not dependent upon the degree of acidity alone. In children in whom Esch. coli was found even without clinical signs of gastroenteritis bactericidal action of the juices was completely absent. Invasion of Esch. coli is assumed to come from above and not from the lower intestines. The presence of Esch. coli in children with gastroenteritis is probably secondary. In these cases a low pH of the stomach juices is generally found.

GLASER, Jerusalem.

THERAPY OF CELIAC DISEASE. W. K. DICKE, Nederl. tijdschr. verlosk. en gynaec. **95**:124 (Jan. 13) 1951.

The author mentions the harmful action of wheat flour on patients with celiac disease; the action is ascribed to a factor localized outside the amylum. This factor occurs also in rye and possibly also in other cereals; perhaps it is also active in subacute intestinal troubles of children. There is much reason to assume that steatorrhea is not caused by a disturbance in resorption but by excretion of fat from the body, especially saturated fatty acids.

In this connection these dietetic measures are recommended for patients with celiac disease: The diet should contain enough calories and be as complete as possible. However, wheat in all forms of preparation should be omitted. Further, the fact should be taken into account that the disturbance of fat metabolism mainly concerns the saturated fatty acids. Olive-oil protein milk should therefore be given instead of ordinary (milk-fat) protein milk.

VAN CREVELD, Amsterdam, Netherlands.

THE INJECTION SYRINGE AND THE RISK OF SERUM HEPATITIS. R. VOORHORST, Nederl. tijdschr. verlosk. en gynaec. **95**:2108 (July 21) 1951.

After having pointed out the risk of transferring serum hepatitis by means of the injection syringe, the author argues that sterilizing injection syringes above 100 C. is not necessary according to our modern views, as it can only give rise to wrong ideas as to the nature of the causal virus. In hospitals each patient should have his own syringe.

VAN CREVELD, Amsterdam, Netherlands.

THE TREATMENT OF CONGENITAL STENOSIS OF THE ESOPHAGUS IN A PREMATURE INFANT. P. M. E. Ph. NYST, Nederl. tijdschr. verlosk. en gynaec. **95**:2333 (Aug. 11) 1951.

The author reports a successful transthoracic esophagotomy in a prematurely born 4-week-old boy after bougienage had failed. At the time of operation the condition was deteriorating, possibly because of exacerbation of a preexisting esophagitis.

VAN CREVELD, Amsterdam, Netherlands.

THE PROGNOSIS OF INFECTIOUS HEPATITIS. J. L. A. PEUTZ, Nederl. tijdschr. verlosk. en gynaec. **96**:807 (April 5) 1952.

The prognosis of infectious hepatitis, according to the author, depends on general but also on early antibiotic treatment. It further depends on different factors which may lead to a relapse (such as infections, trauma, alcohol, wrong diet, and resumption of work). In young infants virus hepatitis rarely takes a serious course.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

CEREBROSPINAL RHINORRHEA FROM CRANIOMASTOID FISTULA. R. H. AMES, W. D. FARMER, and W. H. MILLS, A. M. A. Arch. Otolaryng. **53**:451, 1951.

Leakage of cerebrospinal fluid from the nose is by no means a rare sequel of head trauma. Such a finding is generally regarded as pathognomonic of a communication in the region of the paranasal sinuses or the cribriform plate. It has been shown, however, that in rare instances rhinorrhea may result from a communication between the subarachnoid space and the mastoid or middle ear, the fluid passing through the Eustachian tube and into the nasopharynx.

The authors report such a case of cerebrospinal fluid rhinorrhea resulting from a traumatic craniomastoid fistula in a child of 6 years. Preoperative identification of the site of leakage by catheterization of the Eustachian tube enabled the correct surgical approach to be made and prevented a misdirected exploration of the anterior fossa.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EXPERIMENTAL APPLICATION OF ULTRASONICS TO THE LOCALIZATION OF BRAIN TUMORS: PRELIMINARY REPORT. L. A. FRENCH, J. J. WILD, and D. B. NEAL, J. Neurosurg. **8**:198 (March) 1951.

This report concerns an experimental attempt to apply ultrasonic pulses to the localization of brain tumors. The purpose of these experiments was to examine the possibility of locating, at the time of operation, subcortical neoplasms without the use of brain needles. The experiments were based on the principle that high-frequency sound waves, when driven through tissues, are believed to travel at a rate proportional to the tissue density and to the tissue elasticity. These sound waves are reflected by surfaces involving change in density or elasticity, known as interfaces, and echoes are produced. The time interval before reception of the echo varies according to the texture and thickness of the tissue which the waves traverse. With these known data, it was postulated that when ultrasonic pulses were sent through normal brain tissue the presence of an underlying subcortical neoplasm might be ascertained by measuring this time interval.

It was found that when pulsed ultrasonic vibrations were sent through normal and neoplastic cerebral tissues the texture of the neoplastic cerebral tissue was such that the ultrasonic response was approximately twice that of normal cerebral tissue. Subcortical cerebral neoplasms were located in autopsy material by this method of investigation.

Pulsed ultrasonic vibrations of this frequency did not produce demonstrable damage in the cerebral hemispheres of experimental animals.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SUBDURAL HYGROMA COMPLICATING MENINGOCOCCIC MENINGITIS. S. H. STEINBERG and J. P. MURPHY, J. Neurosurg. **8**:671 (Nov.) 1951.

A case of subdural hygroma with membrane formation complicating meningococcic meningitis in a 5-month-old infant is presented.

From a survey of the literature it is apparent that the occurrence of collections of subdural fluid in cases of acute bacterial meningitis is not uncommon, especially in infants one year of age or under. The most significant indication of the presence of such fluid is persistent fever after apparent bacteriologic cure. Bulging of the anterior fontanel in an infant also should suggest subdural effusion as a possible cause, if meningitis exists or has existed.

The case here reported represents the early development of a subdural hygroma with rapid recurrence of xanthochromic fluid of high protein content after all cultures had been reported sterile. It was believed that encapsulated fluid was present and that surgical intervention, with removal of the membrane, was necessary.

How subdural hygromas with formation of fluid and organization of membranes complicate successfully treated meningitis is difficult to explain. Complete removal of membranes, with freedom for the growing brain to expand thereafter, is the surgical procedure of choice, if needle aspiration of the subdural fluid cannot keep fluid formation in check.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ON CERTAIN ASPECTS OF THE SENSORY ORGANIZATION OF THE HUMAN BRAIN: II. A STUDY OF ROSTRAL DOMINANCE IN CHILDREN. R. COHN, Neurology **1**:119 (March-April) 1951.

Approximately 50 essentially normal children between the ages of 3 and 10 years were examined for evidence of rostral dominance. The subjects were normal with respect to their sensory apparatus, as determined by responses to disparate single cutaneous stimuli. The remarkable finding was that nearly all the children between the ages of 3 and 5½ years showed persistent patterns of response which in all ways resembled the picture observed in adults with irreversibly disturbed brain-cell activity. At the critical age of approximately 6 years in the grossly normal child, the pattern of rostral, or proximal, dominance is no longer evident, or it is evoked (as in the normal adult) in the first or second pair of stimulation. Persistence of the phenomenon of rostral dominance in a well-developed child past the age of 6 years has proved to be fair evidence of mental retardation.

From these results it is obvious that there is an innate pattern of perception of multiple simultaneously applied ipsilateral cutaneous stimuli. When the phenomenon is observed in the adult as part of a disease process, it represents a regression to a more primitive level of perception and adaptation. Moreover, these results indicate that sentiency of, and the resolution of, multiple disparate stimuli is a learned process, and that the apparatus necessary for this learning develops, and is utilizable for this purpose, at the approximate age of 6 years in the normal child.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ELECTROENCEPHALOGRAPHIC EVIDENCE OF THALAMIC AND HYPOTHALAMIC EPILEPSY. E. L. GIBBS and F. A. GIBBS, Neurology **1**:136, 1951.

A search was made for 14- and 6-per-second positive spikes in the electroencephalograms recorded during sleep of 300 control subjects. This pattern was found in eight cases (2%). In a group of 5,000 patients with epilepsy or suspected of having epilepsy, 14- and 6-per-second positive spikes were encountered in 312 cases, or 6%. Such spikes are distorted forms of the normal sleep patterns which have been shown in animals to originate in the thalamus and hypothalamus. The diffuseness of the discharge and the general positivity of the spikes suggest a subcortical origin.

The clinical correlates of 14- and 6-per-second positive spike discharges suggest epileptic disorder in the thalamus and hypothalamus; attacks of pain, rage, and vegetative symptoms are common. As compared with other types of epileptic and epileptiform disorders, 14- and 6-per-second positive spikes are relatively benign. A few discharges of this pattern, particularly in children, in the absence of symptoms should not be regarded too seriously. They are likely to remain asymptomatic, such discharges disappearing with increasing age. When symptoms are present, demonstration of such disorder is important not only as an aid to diagnosis, but as a clue to treatment. Such disorder usually responds well to a combination of diphenylhydantoin (dilantin®) and phenobarbital, or diphenylhydantoin and methylphenylethylhydantoin (mesantoin®).

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CORTISONE AND ACTH AS AN ADJUNCT TO THE SURGERY OF CRANIOPHARYNGIOMAS. FRANC D. INGRAHAM, DONALD D. MATSON, and ROBERT L. MCLAURIN, New England J. Med. **246**:568 (April 10) 1952.

Six children with craniopharyngiomas were operated upon by the authors. Pre- and postoperative care was modified by the use of either corticotropin or cortisone. The schedule of dosages and time intervals involved are given.

These substances were utilized because it was realized that some degree of endocrine dysfunction exists in almost every child with a craniopharyngioma, perhaps because of chronic pressure on the diencephalo-pituitary axis. Operative trauma to the hypothalamus and pituitary produces dramatic and forbidding complications familiar to all neurosurgeons, and it was felt that these were mitigated or abolished by adrenal substitution therapy.

The authors conclude that adrenal substitution therapy should be given to all patients scheduled for exploration of a suspected craniopharyngioma unless specific contraindications exist.

WHEELOCK, Denver.

THE PROBLEM OF CYCLENCEPHALY AND OF CONGENITAL SINGLE LATERAL VENTRICLE. H. ZELLWEGER, Helvet. paediat. acta **7**:98 (March) 1952.

Two cases of congenital single lateral ventricle are described and their relation to cyclencephalus discussed. Photographs of a case of cyclencephalus are shown.

FROM THE AUTHOR'S SUMMARY.

AGENESIA CORPORIS CALLOSI. H. ZELLWEGER, Helvet. paediat. acta **7**:136 (April) 1952.

Seven cases of agenesia corporis callosi are described. The clinical symptoms are oligophrenia, convulsions, changes of the muscle tone, and even spastic diplegia in one case. In one case cataracts and atrophic changes of the eyegrounds occurred.

The pneumencephalographic findings are discussed and arteriograms are shown. In the majority of the cases no branching of the anterior cerebral artery in a callosomarginal and pericallosal artery may be found. In agenesia corporis callosi the anterior cerebral artery divides into several radiating branches. This is according to the radiate configuration of the gyri of the mesial cortex of the hemispheres.

The clinical symptoms occurring in cases of agenesia corporis callosi are due to concomitant cerebral lesions. The pneumoencephalographic finding of agenesia callosi favors the diagnosis of a congenital brain malformation.

FROM THE AUTHOR'S SUMMARY.

PNEUMOCOCCIC MENINGITIS TREATED BY A COMBINATION OF PENICILLIN AND STREPTOMYCIN. E. LASAGNI, Lattante **23**:177 (March) 1952.

Four children, three under 1 year of age and one of 3 years, were treated with intramuscular injections of streptomycin and penicillin and with a sulfonamide (sulfamethazine). Recovery was complete in from 9 to 24 days. The addition of streptomycin to the medication appeared to give better results than when only penicillin and sulfonamide were used (mortality 30%).

HIGGINS, Boston.

HYDATID CYST OF THE BRAIN IN A BOY OF THREE YEARS. EDUARDO C. PALMA, HECTOR C. BAZZANO, EUCLIDES PELUFFO, and JULIO C. BELTRAN, Arch. pediat. Uruguay **23**:102 (Feb.) 1952.

The authors present a case, in a 3-year-old child, of intracerebral hydatid cyst which had produced extensive functional disturbances with diffuse tremors, disturbances in walking and speaking, and a right progressive semiparesthesia. Nine months earlier, the patient had suffered a serious encephalocranial traumatism leaving him with a left facial paralysis. The clinical examination revealed a syndrome of great endocranial hypertension with a bilateral pyramidal syndrome, predominant on the right, and a small cerebellum syndrome. The encephalogram and ventriculograph were not obtainable; instead, incidentally, a pneumocystograph was performed, although contraindicated, which helped establish a diagnosis and the precise localization of the hydatid cyst, situated in the left parietal and occipital lobes. It was very large in size, approximately one-third the cerebral capacity.

The authors noted the contrast between the age of the child and the enormous size of the hydatid and the rapidity of the progress of the symptoms. They suggested that the younger the patient, the greater the effect of the hydatid in the brain.

They point out the benefit of the operative technic used, consisting of (*a*) ample surgical access; (*b*) incision access to the cerebrum of moderate length, in an area fundamentally not functional, proximal to the hydatid; (*c*) protection of the tissues with a double layer of sponges, the lower layer moistened in saline solution and the superficial layer in a 1% formol solution; (*d*) placement of the patient in accentuated Trendelenburg position and inclining the head toward the affected side; (*e*) addition of formol and partial evacuation of the cyst, and (*f*) delivery of the cyst by gravitation and completion of the delivery by instrumental shelling-out of the hydatid.

It was noted that, although the ependymal membrane of the lateral ventricle was greatly displaced by the hydatid, it was, nevertheless, completely undestroyed.

The operative observation showed that the hydatid had produced large destructive lesions in the left cerebral hemisphere.

The postoperative progress was favorable, with great improvement. The endocranial hypertension ceased, permitting the child to regain his speech; there was an almost total disappearance of the cerebellum syndrome and a great improvement in the pyramidal syndrome.

The child is able to stand and walk, although with claudication of his right leg.

FROM THE AUTHORS' SUMMARY.

HEMISPHERECTOMY AS TREATMENT OF CONVULSIONS DUE TO CEREBRAL HEMIATROPHY IN INFANTILE HEMIPLEGIA. S. OBRADOR ALCADE, Arq. neuro-psiquiat. **9**:191, 1951.

The first case of infantile hemiplegia in which an atrophied hemisphere was removed because of convulsions was reported by Obrador Alcade (*Rev. clin. espan.* **36**:172, 1950). In the patient, a girl aged 17, seizures and electroencephalographic changes disappeared in the opposite hemisphere after the operation. Three other patients, 5, 7, and 11 years old, underwent hemispherectomy. All had infantile hemiplegia and epileptic attacks. In two of these patients the hemiplegia was on the left side, and in one, on the right side. All were mentally retarded. All showed electroencephalographic changes on both sides before operation; these changes were somewhat more conspicuous over the atrophied hemisphere. One of the four patients died after the operation. There was no intensification of the hemiplegia in any instance. In a 5-year-old child removal of the left hemisphere was not followed by aphasia; apparently the right hemisphere took over the language function immediately. After the operation seizures disappeared in all the patients, even though no medication was used. Two patients were followed for 20 and 4 months, respectively. The electroencephalogram became normal on the affected side after the operation. The author recommends this operative procedure as a valuable addition to the treatment of convulsions in this condition.

N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

TWO UNUSUAL CASES OF HYDROCEPHALUS IN INFANTS. M. P. A. M. DE GROOD, Nederl. tijdschr. verlosk. en gynaec. **95**:3485 (Nov. 24) 1951.

A description is given of two infants aged 4 months with hydrocephalus, caused in the one by a frontal-basal glioma of the right frontal lobe, and in the other by a subdural empyema situated frontally on the left side. Both children recovered after operative treatment.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

PREFRONTAL LEUCOTOMY IN CHILDREN AND ADOLESCENTS. M. YAHN and S. KRYNSKI, Arq. Assist. psicopat. **16**:15, 1951.

Prefrontal lobotomy was performed on 11 girls, from 9 to 15 years of age, who presented severe behavior problems. The patients were difficult to manage, aggressive, emotionally unstable, and occasionally agitated and had perversions and antisocial tendencies. They had been observed daily in a hospital for about a year. They did not respond to other methods of treatment. The technique of lobotomy used was that of Freeman and Watts. In two patients it was impossible to operate on both sides. Epilepsy, mental deficiency, and psychopathic personality

were represented. The following symptoms were improved by the operation: exhibitionism, destructive tendencies, perversions, impulsiveness, overtalkativeness, epileptic attacks, bouts of anxiety, tendency to become angry readily, attempts to escape and indifference. The results were satisfactory, especially in the psychopathic personalities and the epileptic patients. One patient with psychopathic personality exhibited striking improvement, with social readjustment. Six patients showed marked improvement, which usually consisted in diminution of agitation and antisocial behavior, with a more satisfactory intramural adjustment. Two of the patients were not benefited at all. Two died as a result of postoperative hemorrhage. The authors recommend the use of lobotomy for agitation, antisocial tendencies, and other disturbances in behavior which cannot be controlled in any other way. The series of patients reported is small, but the therapeutic possibilities of lobotomy are indicated. The authors believe that the sequelae of the operation itself should be less severe in younger patients.

N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Ductless Glands; Endocrinology

EFFECT OF INTRASPLENIC OVARIAN GRAFT ON PITUITARY GONADOTROPINS. W. E. ACHILLES and S. H. STURGIS, Endocrinology **49**:720 (Dec.) 1951.

The occurrence of early luteinization in an intrasplenic ovary in a castrated rat afforded the authors an opportunity to reappraise the mechanisms governing storage and release of pituitary gonadotropins and the interactions of ovarian and pituitary hormone secretions.

JACOBSEN, Buffalo.

EFFECTS UPON THE RAT PITUITARY OF A NON-ESTROGENIC OXIDATION PRODUCT OF DIETHYLSTILBESTROL. O. W. SMITH and R. E. VANDERLINDE, Endocrinology **49**:742 (Dec.) 1951.

Dilute aqueous alkaline solutions of diethylstilbestrol lose estrogenic potency but retain their ability to produce the release of adrenotropic and gonadotropic factors from the pituitary of the rat. From such solutions a crystalline compound has been recovered.

JACOBSEN, Buffalo.

ASCORBIC ACID INTAKE AND THE ADRENAL CORTEX. R. C. STEPTO, C. L. PIRANI, C. F. CONSOLAZIO, and J. H. BELL, Endocrinology **49**:755 (Dec.) 1951.

It appears that the reduction of steroid concentration in the adrenal cortex during severe ascorbic-acid deficiency is due to one or a combination of the following two mechanisms: (1) "exhaustion" of the adrenal cortex due to stress and the continuous production of corticosteroids, and (2) diminished production of adrenocorticosteroids in the absence of an adequate concentration of adrenal or otherwise available ascorbic acid.

JACOBSEN, Buffalo.

MECHANISM OF EPINEPHRINE-HYPERGLYCEMIA. M. SOMOGYI, Endocrinology **49**:774 (Dec.) 1951.

The hyperglycemia and glycosuria produced by epinephrine—described half a century ago as "adrenaline diabetes"—has been generally attributed to an increase in the rate of hepatic glycogenolysis. This concept is based on considerable, and apparently unequivocal, experimental evidence. It is well known, for instance, that in hepatectomized animals epinephrine does not produce hyperglycemia and that in the perfused liver and in liver slices in vitro glucose output is increased by epinephrine.

In this paper experimental evidence is submitted to show that depression of the rate of peripheral glucose assimilation by epinephrine action plays an important part in the production of epinephrine hyperglycemia. This aspect has thus far been completely overlooked.

JACOBSEN, Buffalo.

COMPARATIVE VALUE OF CORTISONE, 17-HYDROXYCORTICOSTERONE AND ADRENAL CORTEX EXTRACT GIVEN BY CONTINUOUS INTRAVENOUS INJECTION IN SUSTAINING THE ABILITY OF THE ADRENALECTOMIZED RAT TO WORK. D. J. INGLE, J. E. NEZAMIS, and E. H. MORLEY, Endocrinology **50**:1 (Jan.) 1952.

The average total work done by nonadrenalectomized rats and adrenalectomized animals which received adrenal-cortex extract was significantly greater than the total work of rats treated with optimal amounts of either cortisone or 17-hydroxycorticosterone. Thus it is shown that 17-hydroxycorticosterone does not fully replace the secretion of the animal's own adrenal cortices.

JACOBSEN, Buffalo.

DEMONSTRATION OF A NON-ESTROGENIC UTERINE STIMULATING AND ESTROGEN AUGMENTING SUBSTANCE IN PREGNANT MARES' URINE. H. COHEN and R. W. BATES, Endocrinology **50**:5 (Jan.) 1952.

The data presented in this study demonstrate the presence in pregnant mares' urine of substances which, although estrogenically inactive by themselves, are capable of potentiating the biological effect of estrogens upon the vaginal mucosa of the adult spayed rat.

JACOBSEN, Buffalo.

RELATION OF SOME STEROID HORMONES TO β-GLUCURONIDASE ACTIVITY. E. KNOBIL, Endocrinology **50**:16 (Jan.) 1952.

This report deals with studies of the β-glucuronidase activity of the uterus, mammary gland, prostate gland, and seminal vesicle in relation to the action of estrogens and other steroid hormones.

It is concluded that changes in β-glucuronidase activity are not a generalized phenomenon associated with growth per se and that the evidence presented lends support to the view that these changes may be specifically related to the action of estrogenic hormones.

JACOBSEN, Buffalo.

DIABETOGENIC EFFECT OF GROWTH HORMONE IN THE INTACT FORCE-FED ADRENOCORTICOTROPHIN TREATED RAT. F. L. ENGEL, A. VIAU, W. COGGINS, and W. S. LYNN JR., Endocrinology **50**:100 (Jan.) 1952.

Combined treatment with corticotropin and growth hormone may result in significant hyperglycemia and glycosuria in the intact rat, whereas only minor and irregular glycosuria results from treatment with either hormone alone.

JACOBSEN, Buffalo.

PERIODIC HYPOKALEMIA WITH HYPERELECTROLYTEMIA IN A CASE OF "DYSTROPHIA ADIPOSOGENITALISM." A. PRADER and H. ZELLWEGER, Helvet. paediat. acta **7**:42 (March) 1952.

A case is reported of a mentally deficient, 7-year-old boy with the habitus of adiposogenital dystrophy, who since the second year of life has shown increasing obesity, retardation of growth, and periodic paroxysmal paralysis. Investigation disclosed definitely elevated but markedly fluctuating serum sodium and chloride levels. The paroxysmal attacks fitted the classical pattern of hypokalemic paralysis. There was a tendency toward retention of water, sodium, chloride, and potassium, as well as a less pronounced disturbance of carbohydrate metabolism.

One is thus dealing with a most unusual, incompletely explained metabolic disorder, which, on the basis of numerous findings, appears to be due probably to chronic renal disease. At the same time, there is some evidence suggestive of either a hypophyseal-diencephalic disturbance or an adrenal cortical tumor.

FROM THE AUTHORS' SUMMARY.

FUNCTIONAL TEST OF A CHILD'S ADRENAL CORTEX IN FORTY-EIGHT HOUR TEST WITH ADRENOCORTICOTROPIC HORMONE. F. FERRAZZINI, R. BORTH and R. S. MACH, Helvet. paediat. acta **7**:60 (March) 1952.

The 48-hour test (involving eosinophile count, and determination of 17-ketosteroid and corticosteroid excretion in 24-hour collections of urine, before and during administration of

corticotropin) has been performed on 10 healthy children, 3 to 12 year old. By use of appropriately reduced doses of corticotropin, it has been shown that the 48-hour test gives reliable information on adrenocortical function in children, too.

The effect of corticotropin administration agreed with the results obtained under similar conditions in a previous study, in a group of adult subjects. In particular, the average percentage increase of 17-ketosteroid excretion in children was of the same order as in adults, and no effect of the children's age could be detected. It can be concluded that the capacity to secrete precursors of urinary 17-ketosteroids (the so-called androgenic function) is already fully developed in the adrenal cortex of children.

FROM THE AUTHORS' SUMMARY.

MARCHAND-WATERHOUSE-FRIDERICHSEN SYNDROME. C. PEREZ VICTORIA, Arch. pediat. **2**:39 (July) 1951.

The author says that, although he is opposed to the use of proper names to describe diseases when it is possible to use a more rational method of nomenclature, the syndrome of acute adrenal apoplexy of infancy or acute adrenal insufficiency should be called the Marchand-Waterhouse-Friderichsen syndrome if names are to be used. While Waterhouse described the condition in 1911 and Friderichsen described it in 1918, the first description was given by Marchand in 1880. This author described it as acute Werlhof disease with bilateral hemorrhage in the adrenal capsules.

Most of the patients are children from 2 months to 2 years of age, and there is no evidence of sexual predilection.

The causative agent seems to be the Meningococcus, with a concomitant lability of the adrenal glands. However, cases have been reported in which the hemolytic Streptococcus, Hemophilus influenzae, Neisseria flavus II, Neisseria meningitis, Micrococcus pyogenes var. aureus, and, rarely, Pneumococcus has been the causal organism.

The clinical description is given fully. The value of immediate diagnosis and treatment is obvious.

ALLEN, Santa Fe, N. M.

THE SYNDROME OF WATERHOUSE-FRIDERICHSEN. P. A. A. WETERINGS, Nederl. tijdschr. verlosk. en gynaec. **95**:2040 (July 14) 1951.

The author wishes to demonstrate that the Waterhouse-Friderichsen syndrome is not caused by hemorrhages in the adrenal gland. The complex of symptoms is explained by sepsis and perhaps toxic paralysis of the peripherous autonomous nervous system. An adult female patient (44 years of age) who recovered is described. Adrenal gland preparations were not given. It is important to make an early diagnosis and immediately to institute therapy by means of plasma infusions, polyvalent diphtheria antitoxin and penicillin, a sulfonamide drug, and streptomycin.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

EFFECT OF ASCORBIC ACID, POTASSIUM CHLORIDE FLOODING, AND CORTISONE ON THE COURSE OF FORMALDEHYDE-IRRITATION ARTHRITIS. H. BACCHUS, Endocrinology **49**:789 (Dec.) 1951.

The action of ascorbic acid, potassium-chloride flooding, and cortisone on the course of topical formaldehyde-irritation arthritis was studied. Ascorbic acid excess and KCl flooding hastened the recovery to normal but failed to prevent the initial swelling.

JACOBSEN, Buffalo.

SYMMETRICAL SPONTANEOUS FRACTURES OF UNKNOWN ORIGIN IN INFANTS. J. KUGELMANN, Ann. pædiat. **178**:177 (March) 1952.

The author reports the case of an infant with multiple spontaneous fractures of the long bones and the skull, with a coexistent subdural hematoma and hemorrhages in the endocardium and pericardium. A few similar cases have been recorded in the roentgenological literature by Caffey and Smith. The cause of the spontaneous fractures and the subdural hematomas is unknown.

FROM THE AUTHOR'S SUMMARY.

A Case of Osteogenesis Imperfecta (Vrolik's Type Associated with Other Malformations). Tomas Sala Sanchez, Acta pediat. españ. **9**:1403 (Dec.) 1951.

After a review of the literature of the various forms of osteogenesis imperfecta, the author presents a case history of an infant with Vrolik's type of this disease. The study includes many x-rays of members of the family and of the patient. The hereditary factors are discussed. The interesting differences in this case are the presence of many other malformations and the history of syphilis in the mother, with prenatal treatment resulting in a negative serological reaction in the child.

Several members of the family had intense blue discoloration of the sclera and were very short of stature, suggesting achondroplastic dwarfism. There was no evidence of the prenatal type of fractures such as were found in the patient.

The blood chemistry was typical of precocious osteogenesis imperfecta, with hypercalcemia and hypophosphatemia, the calcium being at one time as high as 19.04 mg. per 100 cc. and the phosphates 1.9 mg.

The other deformities, which are numerous, are not necessarily concomitant with osteogenesis imperfecta. The fact that there are varying degrees of this disease is also noted, although the Lobstein and Vrolik forms are best known. It is commoner in females than in males.

Allen, San Francisco.

Infectious Myositis. J. Bonnet, Nederl. tijdschr. verlosk. en gynaec. **95**:1233 (April 21) 1951.

On the basis of 24 observations by the author, the infectious myositis syndrome, or multiple muscular abscesses, is discussed. The characteristic nature of this disease and its striking resemblance to acute hematogenous osteomyelitis are stressed. The author challenges the opinion that filaria have anything to do with the muscular abscess. The brownish-red color of the pus is ascribed to liberated myohemoglobin, and its strongly acid reaction related by the author to lactic acid or decomposition products of glycogen.

Five extensive disease histories are used for illustrating this conception, the author's own 24 observations having been tabulated.

van Creveld, Amsterdam, Netherlands.

Osteoid Osteoma. G. Bosman and H. N. Hadders, Nederl. tijdschr. verlosk. en gynaec. **96**:865 (April 12) 1952.

Roentgenological examination of a boy aged 3½ years, complaining for 1½ years about his right leg, revealed an anomaly of the os femoris, finally diagnosed as an osteoid osteoma. This skeletal anomaly was first described by Jaffe (1935). In the present case, microscopic examination of the operatively removed tissue confirmed the diagnosis. The histological similarity between the osteoid fibromas occurring in the facial bones of the skull and the osteoid osteoma occurring anywhere else in the skeleton, with the exception of the skull, is stressed. Probably at least a number of these osteoid fibromas are osteoid osteomas.

van Creveld, Amsterdam, Netherlands.

Diseases of Eye

Toxoplasmosis, Histoplasmosis, and Retrolental Fibroplasia—Ocular Aspects in Infancy. L. Dalcet Buxeres, Arch. pediat. **2**:79 (July) 1951.

The author describes the clinical findings in the eyegrounds after a description of the other aspects of toxoplasmosis and histoplasmosis, and emphasizes the need of every pediatrician to be able to examine the infant's eyes for pathology of the fundus.

He also discusses the pathology, possible causes and treatment of retrolental fibroplasia. Corticotropin has not proved effective. The operation of Castroviejo may be more effective.

Allen, San Francisco.

Cutaneous Diseases; Allergy

ALLERGY TO VIRAL AND RICKETTSIAL VACCINES: III. INFLUENCE OF REPEATED INOCULATIONS ON ACQUISITION OF EGG ALLERGY. B. RATNER, S. UNTRACHT, and F. HERTZMARK, New England J. Med. **246**:533 (April 3) 1952.

A series of 319 nonallergic children were given multiple inoculations of mumps-virus and influenza-virus vaccines derived from egg-medium propagation. Although five of these patients acquired dermal sensitivity to egg, they did not show clinical sensitivity.

Twenty children who were sensitive to egg clinically, or no longer sensitive clinically but with a past history of clinical sensitivity, or not clinically sensitive but dermally reactive were given crude or refined influenza vaccine repeatedly. No production or enhancement of clinical sensitivity was noted.

One hundred twenty children who were allergic, but not to egg, were given repeated prophylactic injections and did not acquire egg sensitivity.

The authors conclude that the hazard of sensitization from repeated injections of egg-propagated virus vaccines is negligible.

WHEELOCK, Denver.

KAPOSI'S VARICELLIFORM ERUPTION: DIAGNOSIS AND TREATMENT. A. D. M. JACKSON and J. A. DUDGEON, Great Ormond Street J. **2**:125 (Dec.) 1951.

Clinical and laboratory features of Kaposi's disease are discussed in detail, 16 cases forming the basis for the study. All cases in the series were shown to be due to primary infections with herpes simplex. Methods of diagnosis and treatment are discussed.

McGUIGAN, Evanston, Ill.

EFFECTS OF ADENOTONSILLECTOMIES IN RESPIRATORY ALLERGIES. B. GORELIK, Ann. oto-laryng. **68**:46, 1951.

The following conclusions were derived from a review of 93 cases of respiratory allergies in which adenotonsillectomies had been performed: 1. No improvement was noted among asthmatic patients or persons with vasomotor rhinitis. 2. Vasomotor rhinitis was aggravated in 16 persons, with severe tracheal cough in 7 adults. 3. Vasomotor rhinitis was precipitated in 18 patients who did not have such symptoms before operation. 4. The postoperative return of lymphoid tissue is not of infrequent occurrence in allergic patients who have undergone operation.

VIOLE, Los Angeles [A. M. A. Arch. Otolaryng.].

FREQUENCY OF MERCURY SENSITIZATION AS CAUSE OF INFANTILE ERYTHREDEMA POLYNEUROPATHY (ACRODYNIA). T. BAUMANN, Schweiz. med. Wchnschr. **82**:375 (April 12) 1952.

Of 30 patients with erythredema polyneuropathy observed in the hospital, 13, or about 43%, gave a history of mercury medication in a period up to a half-year before onset. From 17 patients, or about 56%, no history of such medication could be elicited. The number of patients with mercury sensitization in a certain district seen in hospital and private practice diminished progressively in five years, from a total of 41 to one of 12. This recession is attributed to the recognition by physicians, druggists, and the general population of the danger of mercury medication. Treatment of patients with erythredema polyneuropathy with dimercaprol was ineffective.

AMBERG, Rochester, Minn.

KAPOSI'S VARICELLIFORM ERUPTION, OR SIMPLE GENERALIZED HERPES. A. J. ABALLÍ and J. M. CRUZ, Rev. cubana pediat. **20**:197 (April) 1948.

The authors report a typical case in which there were encephalitic manifestations without atopic eczema, but simply with retroauricular intertrigo, in a 7-month-old girl. Inoculation of the cornea of the rabbit with material from the vesicles produced keratoconjunctivitis, followed by fatal encephalitis. Scarification of a healthy area of the patient's skin and inoculation with the vesicle fluid reproduced the lesions. Treatment with sulfonamides tended to prevent secondary infection. The cutaneous lesions were aggravated by trauma and by moisture.

KEITH, Rochester, Minn.

LOCAL APPLICATION OF SULFONAMIDES IN SKIN DISEASES OF CHILDHOOD. W. AURNHAMMER, Med. Klin. **46**:274 (March 2) 1951.

A shaking mixture of 5% *p*-aminobenzene sulfonamide in 77% magnesium salicylate gel with talcum and zinc oxide ("pyodron") was used in various forms of pyoderma in children, such as pemphigus neonatorum and Ritter's disease (dermatitis exfoliativa infantum) in addition to systemic administration of penicillin and sulfonamide therapy. It was also used in cases of periporitis, folliculitis, and, particularly, impetigo contagiosa. It also proved of benefit in many cases of secondary pyoderma.

AMBERG, Rochester, Minn.

ATOSIL SYRUP IN PEDIATRICS. FRITZ HAGGENMULLER, Med. Klin. **47**:320 (March 7) 1952.

The syrup of "atosil" (which is the same as the antihistaminic phenergan,* a phenothiazine derivative) is readily taken by children. It has a definite sedative action, which is of value in some cases with itching. It proved of special benefit in drug and serum exanthems and in urticarial skin eruptions. In cases of chronic eczema and bronchial asthma it was usually ineffective.

AMBERG, Rochester, Minn.

ERYTHREDEMA POLYNEUROPATHY (ACRODYNIA) APPEARING AFTER MILD MERCUROUS CHLORIDE THERAPY, BUT WITHOUT EXCRETION OF MERCURY IN THE URINE, CURED WITH DIMERCAPROL: REPORT OF TWO CASES. R. HOUET, Acta paediat. **41**:158 (March) 1952.

Two cases of erythredema polyneuropathy appearing three and five weeks, respectively, after ingestion of mild mercurous chloride N. F. are reported. Treatment with large amounts of pyridoxine was ineffective, but the two children recovered quickly after dimercaprol therapy. With use of a specific and sensitive method (polarography), no mercury could be found in the urine passed before and during dimercaprol treatment. The author questions whether the Warkany-Fanconi theory that erythredema polyneuropathy is a sensitization to certain mercury salts is not too dogmatic to fit to all cases of the disease.

FROM THE AUTHOR'S SUMMARY.

WEBER-CHRISTIAN DISEASE: A FORM OF SPONTANEOUS PANNICULITIS. R. KOOY, Nederl. tijdschr. geneesk. **94**:1818 (July 1) 1950.

The author reports the occurrence of Weber-Christian disease in two women. He regards the disease as a clinical variant of spontaneous panniculitis and divides the nodular, common panniculitis into three types: (1) panniculitis as a secondary reaction in the vicinity of other processes; (2) primary panniculitis of unknown origin, and (3) "spontaneous" panniculitis, of which he distinguishes three clinical variants: (*a*) Weber-Christian types, (*b*) "nodular vasculitis, and (*c*) the indefinite type.

VAN CREVELD, Amsterdam, Netherlands.

ERYTHEMA EXUDATIVUM MULTIFORME. M. RUITER, Nederl. tijdschr. geneesk. **94**:1927 (July 8) 1950.

The original description of erythema exudativum multiforme by Hebra referred to a benign skin disease of unknown origin. Similar, but atypical, pictures have been described of late under the same name. The skin lesions were not only atypical and much more variable than those seen in erythema exudativum multiforme (herpes iris), but the clinical course differed as well (fever, protracted course, no recidivism). The author suggests that we call this clinical picture the erythema-exudativum-multiforme syndrome to avoid further confusion. It is necessary to limit this syndrome to those cases in which certain requirements concerning the skin lesions are fulfilled.

Erythema exudativum might have an etiologic agent of its own, possibly a virus, while the erythema-exudativum-multiforme syndrome occurs as an allergic reaction to many substances, e. g., drugs, streptococci, and tubercle bacilli.

VAN CREVELD, Amsterdam, Netherlands.

ACRODYNIA AND THE GUILLAIN-BARRÉ SYNDROME COMBINED WITH HYPOTHALAMIC SYMPTOMS. D. P. R. KEIZER, Nederl. tijdschr. geneesk. **94**:2409 (Aug. 19) 1950.

In a one-year-old boy with acrodynia there developed flaccid paralysis of the arms and legs, with loss of reflexes and a normal cell count and elevated albumin content of the spinal fluid. He was treated with dimercaprol. Subsequently he presented unilateral exophthalmos and attacks of sham rage, as seen in hypothalamic disturbances. The patient recovered after treatment with aureomycin.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF HEMANGIOMATA OF THE SKIN, ESPECIALLY NEVUS FLAMMEUS. J. R. PRAKKEN, M. NIJKERK, and C. VROEGE, Nederl. tijdschr. verlosk. en gynaec. **95**:1888 (June 30) 1951.

When following up 99 patients with nevus flammeus treated with grenz rays, the authors found the results good in a considerable portion of the cases, especially when the treatment had taken place at an early age. Sequelae caused by the treatment were observed in none of these patients, although the chance of a permanent pigmentation arising is mentioned, on account of an observation on a young patient who had been treated with grenz rays because of a strawberry mark.

VAN CREVELD, Amsterdam, Netherlands.

THE EOSINOPHILIC GRANULOMAS OF THE SKIN. M. J. WOERDEMAN, Nederl. tijdschr. verlosk. en gynaec. **96**:140 (Jan. 19) 1952.

The author proposes a classification of the eosinophilic granulomas of the skin into five groups. He discusses more extensively the cutaneous manifestations of eosinophilic granuloma of bone, Hand-Schüller-Christian disease and the disease of Abt-Letterer-Siwe. (For this group of diseases Pinkus and others in 1949 proposed the name reticulogranuloma.) Two cases of reticulogranuloma eosinophilicum cutis simplex are described; they differ from the cases so far described, as there is only one lesion, namely a solitary nodule.

VAN CREVELD, Amsterdam, Netherlands.

SKIN ERUPTIONS CAUSED BY BARBITURATES. L. VAN DER LUGT, Nederl. tijdschr. verlosk. en gynaec. **96**:550, 1952.

Four cases of toxicoderma due to taking of butethal and phenobarbital are described. The author succeeded in transmitting the formed antibodies.

VAN CREVELD, Amsterdam, Netherlands.

MERCURY POISONING AS CAUSE OF ACRODYNIA. J. DRUKKER, Nederl. tijdschr. verlosk. en gynaec. **96**:884 (April 12) 1952.

Seven cases are described of acrodynia caused by mercury poisoning in children, in four of whom the urine contained mercury. Three out of four patients treated with dimercaprol ("BAL") improved shortly afterward.

Mercury in any form should be withheld from children.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

MODERN TRENDS IN CLEFT LIP AND PALATE SURGERY. R. N. SINHA, Indian J. Pediat. **18**:154 (Oct.) 1951.

The author describes very briefly the most commonly used technique for repair of harelip and cleft palate. Adequate speech is the primary result to be sought in cleft palate surgery.

McGUIGAN, Evanston, Ill.

Teeth and Dentistry

INDICATIONS AND RESULTS OF DENTOMAXILLOFACIAL ORTHOPEDIC THERAPY. J. T. QUINTERO, M. CHASSIGNOL and J. E. HESKIA, Pédiatrie **39**:725, 1950.

It is an often-neglected duty of the pediatrician to supervise the child's habits with a view to preventing dental malposition. The optimal time of treatment may be before 9 years or after 12 years, but should not be undertaken during this period, which is the time of development for the premolars. The treatment consists of a period of setting and a period of retention, which together may be up to two to three years in length. The upper age limit when results can still be expected is 15 to 18 years. Functional and cosmetic results, as well as an improvement in the general condition of the child, justify the prolonged treatment.

GLASER, Jerusalem.

HYGIENE AND TREATMENT OF CHILDREN'S TEETH. M. MAZET, Pédiatrie **39**:733, 1950.

Prophylaxis of dental caries in children should start during pregnancy, when the anlage for some teeth is laid down. Dietary guidance of the pregnant woman is as important as that of the child during the period of eruption, up to 3 years of age. From 4 to 7 years of age the duty of dental supervision is shared by pediatrician and dentist, inasmuch as active treatment of caries begins at this age. From 7 to 15 years the responsibility of dental care lies with the dentist or the dental surgeon. From a dental point of view, treatment of caries in temporary teeth should be similar to the treatment of permanent teeth.

GLASER, Jerusalem.

INFANTILE MELANODONTIA. G. BELTRAMI, Pédiatrie **39**:751, 1950.

A rare and little known finding in children of white, and finally black, discoloration of the teeth, with abrasion of the surface and final complete loss of the crown, is described. The cause is unknown. The condition is painless and has no influence upon the development of the permanent teeth.

GLASER, Jerusalem.

ADMINISTRATION OF ACTH IN BURNS. I. VAN DER HAL, Nederl. tijdschr. verlosk. en gynaec. **95**:2955 (Oct. 6) 1951.

Experience in a young patient with serious burns, to whom corticotropin was administered, confirmed descriptions elsewhere. The general condition improves rapidly, infectious processes, however, being more likely to occur.

It seems recommendable in cases of serious burns to administer corticotropin just for a short period, and only in case of intensive protection against secondary infections by prophylactic administration of antibiotics, while the usual treatment for shock should not be omitted. Wound healing (and/or transplantation) may be promoted by administering corticotropin again at a later stage of the process.

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

VARIOUS ASPECTS OF ADOLESCENCE. J. R. GALLAGHER, J. Pediat. **39**:532 (Nov.) 1951.

Gallagher, perhaps our outstanding authority on adolescent boys, discusses many of the physical, mental, and emotional problems of this age period. There is no "normal" boy.

MACDONALD, Pittsburgh.

FROSTBITE FROM PROLONGED EXPOSURE TO MODERATE TEMPERATURES. N. GOLDSTEIN and MARY PARKE MANNING, J. Pediat. **39**:616 (Nov.) 1951.

An 8-year-old Negro girl with congestive heart failure was placed in a Barach-type oxygen tent. Her unprotected right ear, close to the oxygen inlet, was exposed to a constant jet of air cooled to 65 F. After six days symptoms of frostbite developed in the pinna of the ear. Two months later the major portion of the involved helix had sloughed.

MACDONALD, Pittsburgh.

BACTERIOSTATIC, GERMICIDAL, AND SANITIZING ACTION OF QUATERNARY AMMONIUM COMPOUNDS ON TEXTILES. M. A. LATLIEF, M. T. GOLDSMITH, J. L. FRIEDL, and L. S. STUART, J. Pediat. **39**:730 (Dec.) 1951.

The behavior of diaper disinfectants is erratic. The authors report that to provide sufficient quaternary ammonium compound to prevent ammonia formation in diapers there must be accurate control of the concentration of the specific quaternary salt, the temperature of application, and the exposure time.

MACDONALD, Pittsburgh.

CORTICOTROPIN AND CORTISONE IN PEDIATRIC PRACTICE. W. P. BARBA II and J. CRAVIOTO-MUNOZ, J. Pediat. **39**:750 (Dec.) 1951.

Barba and Cravioto-Munoz present a detailed summary of the physiologic actions of corticotropin and cortisone, along with indications and contraindications for the use of these agents. There are few definite indications for the use of corticotropin or cortisone. These compounds have two basic functions in clinical medicine: first, to replace physiologically a deficient endogenous hormone and, second, to block the manifestations of, but not significantly to alter, an underlying disease process. They should not be used in clinical pediatrics unless the expected beneficial results warrant the risk involved. They should not be used unless careful clinical and laboratory observations are available in safeguarding against serious toxic effects.

MACDONALD, Pittsburgh.

TECHNICAL PROBLEMS IN METABOLIC INVESTIGATIONS IN CHILDHOOD. M. E. EDMUNDS, Arch. Dis. Childhood **25**:254 (Sept.) 1950.

A metabolic bed is described, and methods of collecting urine quantitatively from premature and full-term infants are presented. The advantages and disadvantages of each method are discussed. An investigation of the efficiency of carmine as a marker is described.

KELLY, Milwaukee.

LEAD POISONING IN INFANCY. N. S. CLARK, Arch. Dis. Childhood **25**:297 (Sept.) 1950.

The author comments on the infrequency in the British literature of case records of lead poisoning in infancy. A case of lead poisoning with encephalopathy in an infant is described. Although the lead was derived from the domestic water supply, the other members of the family showed no overt signs of poisoning. The changes in the bones which on x-ray examination first drew attention to the diagnosis are described.

KELLY, Milwaukee.

ABSCESS OF THE LIVER AND PERITONITIS SECONDARY TO ASCARIASIS. FLORENCIO BAEZA DONOSO, Rev. chilena pediat. **23**:82 (Feb.) 1952.

The author reports a case of an 18-month-old infant who had purulent pericarditis and peritonitis secondary to the rupture of multiple liver abscesses. The presence of many Ascarides in the intrahepatic bile ducts and the suppurative angiocolitis allow one to suspect that these parasites have caused the liver abscesses and secondarily the peritonitis.

FROM THE AUTHOR'S SUMMARY.

NITROUS OXIDE IN PEDIATRICS. WOLFGANG VOGT, Monatsschr. Kinderh. **99**:189 (May) 1951.

Inhalation of a mixture of 85% nitrous oxide and 15% oxygen for analgesia in minor surgical procedures such as thoracenteses and small incisions, also for repeated lumbar punctures in children with tuberculous meningitis, proved to be safe and effective.

HARTENSTEIN, United States Army.

A CHRONOLOGICAL TABLE OF THE EVOLUTION OF PEDIATRICS AND CHILD HEALTH. A. CESAR ANJO, Arq. pediat. **24**:7 (Nov.) 1951.

The author lists the important medical discoveries and writings beginning with Hippocrates and ending in 1946 that have, in his opinion, significantly affected the course and development of pediatrics and child welfare.

CHRISTOPHERSON, Wilmette, Ill.

DIFFERENTIAL DIAGNOSIS OF BOECK'S SARCOID. K. KNUTH, Ztschr. Kinderh. **68**:318 (No. 4) 1950.

A case of Boeck's sarcoid in a 17-month-old child with miliary skin and lung lesions, hepatosplenomegaly, and yellowish-brown pigmentation, is described and proved by autopsy. In a review of the literature only few cases can be found reported in children under 13 years of age. Differential diagnosis between Beck's sarcoid, tuberculosis, syphilis and the storage diseases is discussed.

GLASER, Jerusalem.

THREE FORMS OF MERCURIAL POISONING. R. PEETERS, Acta paediat. belg. **4**:233, 1950.

Two brothers, 2½ and 3½ years old, drank mercuric oxycyanate and came down with signs of mercurial nephrosis (lower nephron nephrosis). Treatment consisted of administration of 2.5 mg. of dimercaprol per kilogram of body weight in 48 hours; both recovered.

A 2-year-old child received three doses of mild mercurous chloride N. F. orally on alternating days and became ill with fever and a partially scarlatiniform, partially morbilliform eruption. The child recovered spontaneously.

Three cases of acrodynia are reported. In two a history of ingestion of mild mercurous chloride was evident; in the third the mother had given a vermifuge, the composition of which could not be determined.

The author suggests that, although mercury may be a causative factor in acrodynia, predisposition of certain cases must be assumed because of the large number of children who receive mercurials and the low incidence of acrodynia.

GLASER, Jerusalem.

AEROSOL AND PERORAL PENICILLIN TREATMENT IN INFANTS AND YOUNG CHILDREN. P. KARLBERG, G. STERNER, and G. WALLMARK, Svenska läk-tidning **47**:1122 (May 12) 1950.

Thirty children, from newborn infants to children 3 years of age, suffering from an acute catarrhal infection of the lungs and respiratory tract were given aerosol penicillin treatment, in a dose of 50,000 I. U. three to six times a day, each treatment lasting 10 minutes. The blood level of penicillin corresponded fairly well with that following injection of 10,000 I. U. and was sufficiently high (>0.06 I. U. per milliliter) to produce an antibacterial effect for three hours.

With children below one year of age penicillin may be administered by mouth, as shown by observation on a series of 33 in this age group. It is recommended that the drug be given in a glucose solution between or shortly before meals. The dose varies according to age and type of disease, from 20,000 to 50,000 I. U., given three to five times a day.

WALLGREN, Stockholm, Sweden.

PERORAL CALCIUM ADMINISTRATION IN INFANTS. O. MELLANDER, Upsala läkaref. förh. **55**:247 (Dec.) 1950.

Balance tests on infants showed that calcium bound to phosphopeptides from cow's-milk casein could be absorbed from the digestive tract. Calcium in this form could also be shown to promote bone calcification in rachitic children, in some cases without concomitant administration of vitamin D.

WALLGREN, Stockholm, Sweden.

CAUSE OF HEMORRHAGES DURING THE USE OF AMINOPTERIN. S. VAN CREVELD, M. M. P. PAULSSEN, and S. K. TENG, Nederl. tijdschr. verlosk. en gynaec. **95**:374 (Feb. 3) 1951.

The changes in plasma AC globulin after administration of "aminopterin" (4-aminopteroyl glutamic acid) were studied in two patients. The conclusion is drawn that decrease of this clotting factor may be a cause of the obscure hemorrhages occurring often during this treatment.

VAN CREVELD, Amsterdam, Netherlands.

News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified by the American Board of Pediatrics, Inc., after examinations held in Chicago on Oct. 24, 25, and 26, 1952:

Arnold, Jesse H., Greenville, S. C.
Balsley, Robert E., Reidsville, N. C.
Beazley, Luther A., Jr., Donelson, Tenn.
Benton, Charles Richard, Pensacola, Fla.
Berggreen, Raymond G., Mason City, Iowa.
Bielstein, Charles M., Oklahoma City.
Bikoff, William H., Brooklyn.
Boger, Richard Edwin, Atlanta.
Bregman, Larry, Camp Gordon, Ga.
Brown, Spencer Franklin, Minneapolis.
Budwig, Ira A., Jr., El Paso, Texas.
Cohen, Bennett Philip, Dayton, Ohio.
Cohnberg, Rosellen Elaine, Monett, Mo.
Cornblath, Marvin, Army Chem. Center, Md.
Craig, Reuben Allen, Kokomo, Ind.
Cunningham, Guy Clayton, Paducah, Ky.
Curbo, James Rollins, Houston, Texas.
Daeschner, Charles W., Jr., Houston, Texas.
Easton, Robert Sidney, Peoria, Ill.
Fairchild, John Phillip, Fort Bragg, N. C.
Ford, George David, Galveston, Texas.
Forsyth, William B., Rochester, N. Y.
Freeman, Charles W., Oklahoma City.
Gholz, Anthony Carroll, Port Huron, Mich.
Graves, John, Dubuque, Iowa.
Hall, Thomas Newton, Modesto, Calif.
Hartman, Owen W., Chambersburg, Pa.
Henken, William Francis, Racine, Wis.
Husson, George S., Baltimore.
Irby, Addison Craft, Fort Scott, Kan.
Johns, Donald Conrad, Grand Rapids, Mich.
Jones, William John, Wyandotte, Mich.
Kaufman, Harry, Miami Beach, Fla.
Kelly, James J., Covington, Ky.
Kinsey, William C., Erie, Pa.
Korn, Wallace, Gunter Air Force Base, Ala.
Lahey, Marion Eugene, Cincinnati.
Leer, John A., Jr., York, Pa.
Leiter, Forrest Carlton, Dearborn, Mich.
Lesser, Raymond E., Park Forest, Ill.
Levy, David Benjamin, Detroit.
Lund, George Weldon, Minneapolis.
Lynxwiler, Chester Paul, St. Louis.
McCall, Fred Carlton, Bristol, Tenn.
Marrs, Theodore C., Montgomery, Ala.
Martin, Robert E., Arlington, Va.
Merritt, Floyd Benjamin, Dubuque, Iowa.
Metcalf, Lawrence E., Asheville, N. C.
Nabers, Hugh Comer, Birmingham, Ala.
Oberst, Byron Bay, Omaha, Neb.
Parker, Homer Sidney, Chicago.
Plotnick, Irving Robert, Chicago.
Plummer, George W., Portsmouth, Va.
Pollard, Vincent D., Decatur, Ill.
Purcell, Howard Malcolm, Phoenix, Ariz.
Raiford, Fletcher Lindsay, Hendersonville, N. C.
Rice, Margaret Mary, New York.
Robbins, Anne S., Toledo, Ohio.
Roett, Catherine Juanita Elizabeth, Houston, Texas.
Rozenfeld, Irving H., Oklahoma City.
Salisbury, Carolyn S., Detroit.
Schulick, Raymond Murray, Camp Crowder, Mo.
Segall, Harold, Arlington, Va.
Severson, C. Henry, Kenmore, N. Y.
Sheridan, F. Michael, Royal Oak, Mich.
Simon, Richard DeLoe, Toledo, Ohio.
Smith, Hugo Dunlap, Camp Breckenridge, Ky.
Stayer, Irene Moszkowska, Roanoke, Va.
Steinhart, Jacob M., Buffalo.
Stephens, Edgar Walter, West Palm Beach, Fla.
Stern, Aaron M., Ann Arbor, Mich.
Stewart, William Huffman, Thomasville, Ga.
Strain, Thomas Everett, Jr., Shreveport, La.
Swisher, Marion R., Marion, Ohio.
Tancredi, Chester, San Diego, Calif.
Tenney, Horace K., III, Madison, Wis.
Thornfeldt, Robert Ernest, Battle Creek, Mich.
Traisman, Howard Sevin, Chicago.
Watkins, Carlton Gunter, Fort Bragg, N. C.
White, William Elliott, Morganton, N. C.
Yudkin, Gerald Simeon, Kansas City, Kan.

ANNOUNCEMENTS

Coming Examinations to Be Held by the American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold written examinations under local monitors on Friday, Jan. 16, 1953. This is the only written examination which will be given during 1953. Oral examinations will be held on Feb. 20, 21, and 22, 1953, in Baltimore; on March 27, 28, and 29, 1953, in Memphis; on May 1, 2, and 3, 1953, in Philadephia; in June, 1953, in Detroit or Ann Arbor, Mich.; on Oct. 9, 10, and 11, 1953 (tentative, place undecided), and in November, 1953, in Indianapolis.

Twenty-First Annual Benjamin Knox Rachford Lectures.—Paul György, M.D., professor of nutrition in pediatrics at the University of Pennsylvania School of Medicine and pediatrician-in-chief at the Hospital of the University of Pennsylvania, will deliver the 21st annual series of the Benjamin Knox Rachford Lectureships on Tuesday, Feb. 10, and Wednesday, Feb. 11, 1953, at 8:30 p. m., in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. The titles of his lectures are (1) "Human Milk versus Cow's Milk in Infant Nutrition" and (2) "Protein Nutrition and the Liver."

Officers Elected for American Academy for Cerebral Palsy.—At the last meeting of the American Academy for Cerebral Palsy, held in Durham, N. C., Oct. 2 to 4, 1952, the following officers were elected: Arnold Gesell, M.D., president; Meyer A. Perlstein, M.D., president-elect, and Harry E. Barnett, M.D., secretary-treasurer.

Postgraduate Course on Adolescence.—"Adolescence" will be the theme of this year's intensive postgraduate refresher course for pediatricians February 23d through 27th, inclusive, at Tulane University of Louisiana School of Medicine. Dr. Joseph A. Johnston, of the Henry Ford Hospital, will serve as guest lecturer; a full program has been arranged covering nutritional, endocrinologic, psychiatric, gynecologic, orthopedic, dental, dermatologic, and general medical problems. Those interested may secure full information and application forms by addressing the Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans.

Course on Practical Aspects of Common Endocrine and Metabolic Disorders of Children and Adolescents.—An intensive course on practical aspects of common endocrine and metabolic disorders of children and adolescents will be given by Dr. Nathan B. Talbot and associates under the auspices of the Harvard Medical School at the Massachusetts General Hospital on April 16 to 18, 1953, which are the three days immediately preceding the Boston meeting of the American Academy of Pediatrics. Those interested should write to the Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15. Attendance will be limited.

PERSONAL

Appointment for Dr. William A. Reilly.—Dr. William A. Reilly, director of the Radioisotope unit at Fort Miley in San Francisco, has been appointed clinical professor of pediatrics at the University of California Medical School.

Books

Diagnostic and Experimental Methods in Tuberculosis. By Henry Stuart Willis, M.D., and Martin Marc Cummings, M.D. Price, $10.00. Pp. 373, 40 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

In the preface to the second edition, the authors state that their purpose in bringing out another book on tuberculosis is to place in the hands of the physician, the public health worker, the medical student, and the technologist "information on the essential features of the laboratory approach to tuberculosis." This the book does in a rather unique way for a treatise on tuberculosis. It is not purely a laboratory manual, nor is it the usual text in which clinical and roentgenological features of tuberculosis predominate with laboratory procedures appended. Rather, emphasis throughout is on the tuberculosis bacillus itself; how to obtain it from the sputum, from other body fluids, and by biopsy; characteristics of the bacillus; its demonstration by staining, culture, and animal inoculation methods; differentiation from nonpathogenic acid-fast bacteria; vaccination (BCG); methods of determining sensitivity and resistance of the tubercle bacillus to streptomycin and paraaminosalicylic acid (PAS); tuberculin testing, and finally several chapters upon methods of study of tuberculosis experimentally produced in animals.

Thus the approach to the tuberculosis problem in this volume is to provide the clinician and the laboratory worker with information and technics which, once tuberculosis is suspected, will lead to the "clincher" in the diagnosis—demonstration of Mycobacterium tuberculosis. While it may be troublesome, and frequently is, to attain this goal, nevertheless it must be admitted that there is no substitute for diagnostic accuracy.

An extensive bibliography (501 references) is included. Details of the preparation of various stains and culture media together with the technics of their use are set forth. Also described are the various methods of inoculating laboratory animals, and later in the section on experimental methods autopsy technic and pathological appearance of the tuberculous animal are described. Appropriate illustrations enhance the text material.

The eminence of the authors in the field of tuberculosis assures the reader of the scientific accuracy of the statements made. In the opinion of the reviewer, this is an important and valuable reference book for anyone who is interested in tuberculosis.

Some Rare Manifestations of Metabolic Bone Disease. By I. Snapper, M.D. Price, $3.00. Pp. 97, with 18 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

Dr. Snapper presents case histories illustrating metabolic bone disease in which the skeletal changes, if present at all, remain in the background, while the prominent symptoms are related to metabolic disturbances. Five cases of hyperparathyroidism were presented as (1) nephrolithiasis, (2) renal calcinosis, (3) polyuria resembling diabetes insipidus, (4) gastrointestinal disturbance, and (5) mental confusion. The combination of multiple myeloma and amyloidosis is described in two cases. There are diagnostic difficulties even when hyperparathyroidism accompanied by von Recklinghausen's disease as osteitis fibrosa is also the sequel to rapid demineralization of bone from other causes. The biochemical syndrome of von Recklinghausen's disease (hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia) is not pathognomonic, but the diagnosis should not be made in its absence. Atypical cases of Paget's disease, postmenopausal osteoporosis and multiple myeloma, are presented which illustrate the problem of differential diagnosis.

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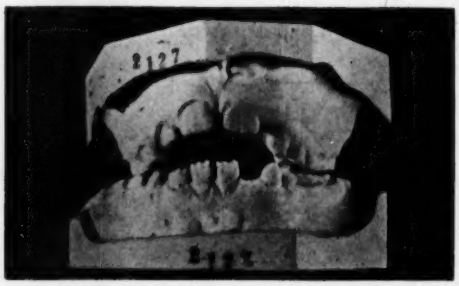

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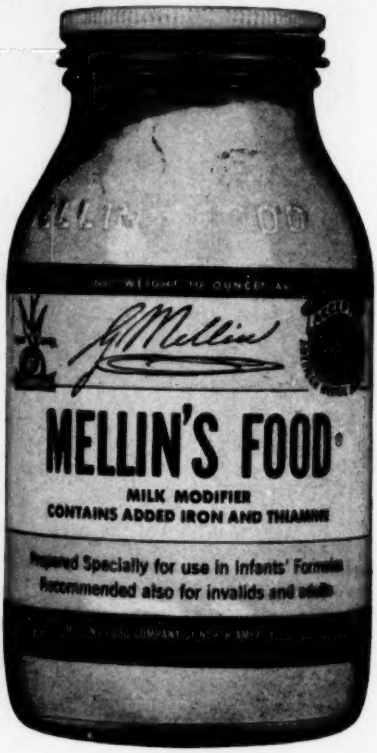

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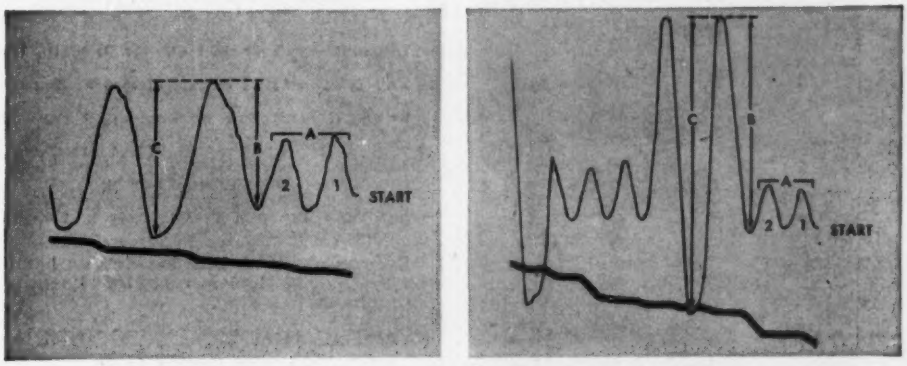

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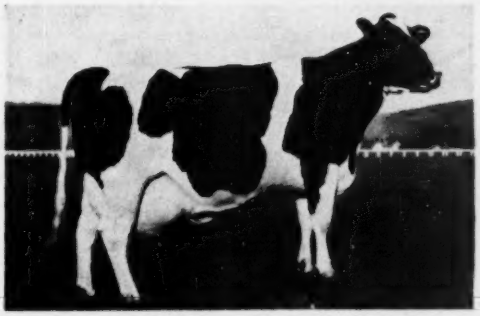

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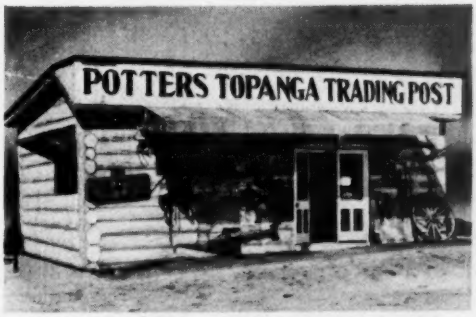

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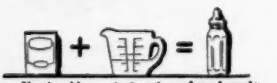

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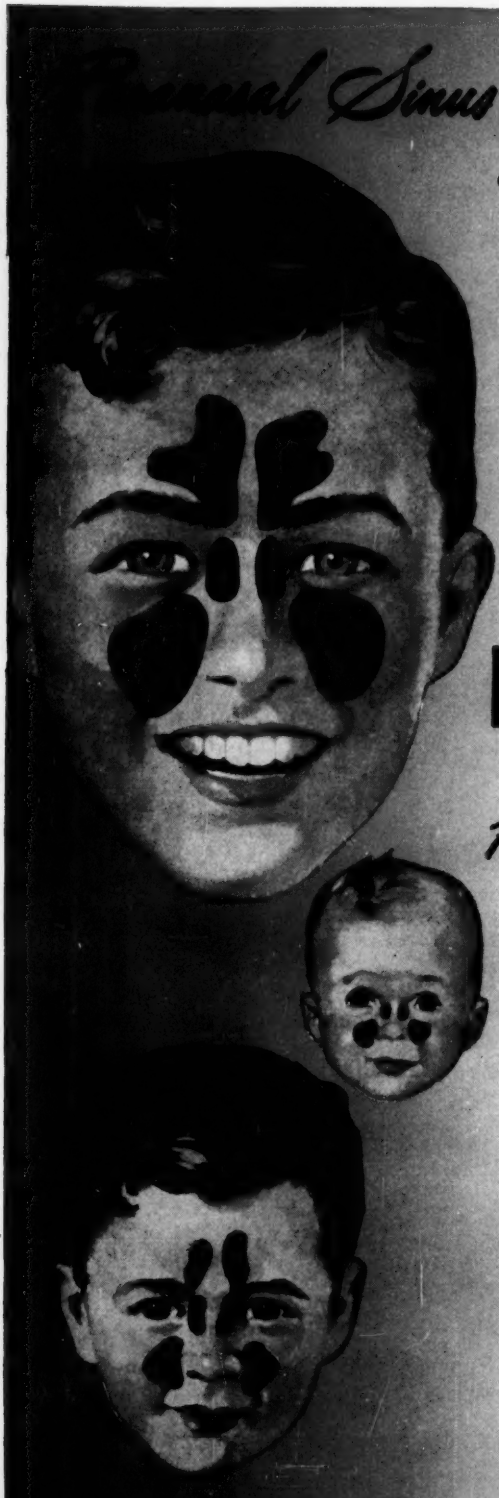

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